Declaration

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Maria Luisa Aiello

Table of contents

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Finally, but by no means least, thanks to my family: my parents and my brothers for their constant encouragement. I dedicate this thesis to them.

Abstract

Expansion of the scope of catalytic cycloaddition reactions involving enolisable anhydrides to various Michael acceptors as electrophiles has been investigated. The reaction between homophthalic anhydrides and *α-β* unsaturated carbonyl compounds under mild conditions has furnished dihydroisocoumarin products bearing 3 stereocentres (one being quaternary) in good yield, excellent diastereoselectivity, however with poor enantiocontrol. Efforts were exhausted in the development of optimal catalytic conditions for this reaction and as such it was deemed impossible to achieve good stereocontrol without being able to reduce the rate of uncatalysed background reaction.

A novel reaction in which a racemic *α*-branched aldehyde is kinetically resolved by bifunctional cinchona alkaloid derived organocatalysts while simultaneously forming 3 stereocentre-containing dihydroisocoumarin acids with good diastereoselectivity and excellent enantiocontrol is also reported. Testing of various aldehydes in this reaction showed that the use of alkyl substituted *α*-branched aldehydes in the presence of bifunctional cinchona alkaloid-derived organocatalyst bearing a bulky aromatic substituent furnished good levels of *dr* and *ee*.

Inspired by the success of the first catalytic asymmetric cycloaddition reaction between aldehydes and homophthalic anhydrides an investigation into the possibility of reversing the high levels of *trans*-diastereoselectivity previously observed was carried out by choice of a bulky substituted squaramide-based catalyst. This process provided one pot access to functionalised *cis*-dihydroisocoumarins in high yields and excellent optical purity-products which are recognised as privileged core structures in natural compounds with diverse pharmacological activities. In order to rationalise the stereochemical outcome, computational studies in support of the experimental data were carried out by a collaborator. The methodology developed was later extended to the use of aryl succinic anhydrides as a means of accessing paraconic acid derivatives (another privileged core present in natural products exhibiting a broad spectrum of biological activity) in a highly enantioselective fashion.

The catalytic asymmetric cycloaddition between phenyl glutaconic anhydride and hindered branched aldehydes was also explored. The results obtained demonstrated the feasibility of the process which allows for the synthesis of 3,4-dihydropyrone derivatives bearing two stereocentres as potential precursors to natural products of the kavalactone family.

Finally, the synthesis and employment of bifunctional iminophosphorane catalysts in formal cycloaddition reactions involving less reactive anhydrides and aldehydes was examined. The catalytic cycloaddition between phenyl glutaconic anhydride and aromatic aldehydes was made possible for the first time, and further optimisation of the cycloaddition with aliphatic aldehydes is also reported.

Abbreviations

abs. config.	Absolute configuration
Ac	Acetyl
AcOH	Acetic acid
APCI	Atmospheric-pressure chemical ionization
app. t	Apparent triplet
Ar	Aryl
B	Base
b.p.	Boiling point
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
bs	Broad singlet
c-	*cyclo*-
cat.	Catalyst
CIP	Cahn–Ingold–Prelog
COD	1,5-Cyclooctadiene
conc.	Concentrated
conv.	Conversion
CSP	Chiral stationary phase
d	Days
d	Doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DCC	N,N'-dicyclohexylcarbodiimide
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
DIAD	Diisopropyl azodicarboxylate
DIPAMP	Ethane-1,2-diylbis[(2-methoxyphenyl)phenylphosphane]
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DPPA	Diphenylphosphoryl azide
Dr	Diastereomeric ratio
E	Electrophile
Ee	Enantiomeric excess
EI	Electron ionisation
equiv.	Equivalent
ESI	Electrospray ionization
Et	Ethyl
EtOAc	Ethyl acetate

EtOH	Ethanol
EWG	Electron withdrawing group
h	Hours
$HNEt_2$	Diethyl amine
HOMO	Highest occupied molecular orbital
HPLC	High Performance Liquid Chromatography
HRMS	High-resolution mass spectrometry
i-	*iso*-
IPA	*iso*-Propyl alcohol
i-Pr	Isopropyl
i-Pr_2NEt	*N*,*N'*-Diisopropylethylamine (Hünig's base)
i-PrOH	2-propanol
IR	Infrared
IUPAC	International Union of Pure and Applied Chemistry
KHMDS	Potassium bis(trimethylsilyl)amide
LA	Lewis acid
LDA	Lithium diisopropylamide
L-DOPA	L-3,4-DIHYDROXYPHENYLALANINE
LiHMDS	Lithium bis(trimethylsilyl)amide
lit.	Literature
LUMO	Lowest unoccupied molecular orbital
m	Multiplet
m-	*meta*-
m.p.	Melting point
m/*z*	Mass/Charge
Me	Methyl
MeOH	Methanol
min	Minutes
mol. sieves	Molecular sieves
MTBE	Methyl-*tert*-butyl ether
MW	Microwave
n-	*normal*-
NaOAc	Sodium acetate
NEt_3	Triethylamine
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
Nu	Nucleophile
o-	*ortho*-
OAc	Acetate
p-	*para*-
Ph	Phenyl

Pr	Propyl
prod.	Product
q	Quartet
R_f	Retardation factor
rt	Room temperature
s	Singlet
t	Triplet
t-	*tert*-
t-Bu	*tert*-Butyl
t-BuOH	*tert*-Butyl alcohol
temp.	Temperature
tert-	*tertiary*-
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMG	1,1,3,3-Tetramethylguanidine
TMS	Trimethylsilyl
$TMSCHN_2$	Trimethylsilyl diazomethane
TMSCN	Trimethylsilyl cyanide
UV	Ultraviolet
v/*v*	Volume/Volume
w/*v*	Weight/Volume

1. Introduction

In recent years, interest in asymmetric synthesis as a method for obtaining enantiomerically enriched compounds has grown rapidily. The widespread demand for chiral molecules in areas ranging from medicine to materials science has stimulated intensive research into the development of various means of accessing single-enantiomer compounds.

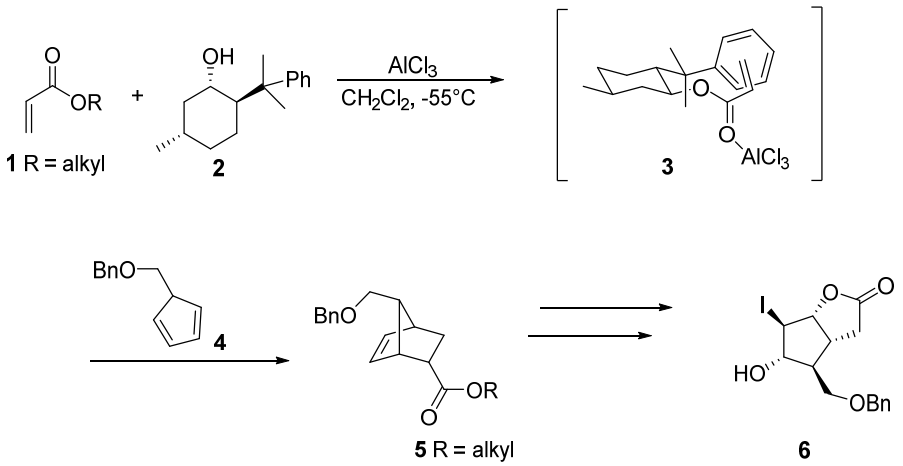
The four main synthetic strategies[1] are outlined below:

- Resolution of racemates
- Employment of chiral pool compounds
- The use of a chiral auxiliary
- Asymmetric catalysis

The resolution of a racemic mixture[2] is one of the oldest methods used by chemists to obtain enantiopure compounds from an equimolar mixture of two enantiomers. It was performed in 1848 by the French chemist and microbiologist Louis Pasteur,[3] who first manually separated two kinds of hemihedral crystals of racemic tartaric acid salts, leading to the discovery of chirality[4] and spontaneous resolution.[5] In more recent times, resolution of a racemic mixture typically involves the reaction of racemic substrate with a chiral resolving agent which leads to the formation of two separable diastereoisomers. The main disadvantages associated with this technique are the addition of two extra steps for the formation and cleavage of the diastereomeric pairs and a maximum theoretical yield of 50% for each enantiomer. Another common methodology is to employ chirally resolved starting materials (so called 'chiral pool'[6,7,8]), which can be sourced from nature, such as amino acids, carbohydrates and alkaloids. They can be used as reagents in natural product synthesis and other synthetic strategies in which the final product and the chiral compound used are structurally similar. This approach affords products of high optical purity, in high yield, through an intramolecular transfer of chiral information. As chiral pool materials are required in stoichiometric amounts, it can be sometimes expensive.

Chiral auxiliaries gained tremendous popularity 30 years ago when E. J. Corey and co-workers carried out an asymmetric Diels-Alder[9] cycloaddition involving 8-phenylmentholacrylate ester Lewis acid complex **3** and 5-benzyloxymethylcyclopentadiene (**4**) in the preparation of prostaglandin intermediate **6**

(Scheme 1.1).[10] The chiral auxiliary **2** plays a key role in the formation of the *endo* adduct **5**, by blocking the *re*-face of acrylate ester **1**, which forces the cycloaddition to occur at the *si*-face of the olefin.



Scheme 1.1 Employment of 8-phenylmenthol (**2**) in the synthetic route of prostaglandin intermediate **6**.

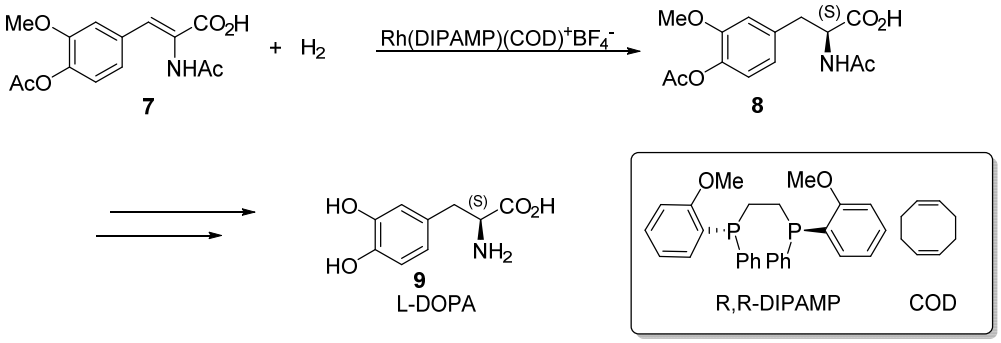
Since then, Evans' oxazolidinones[11] and Oppolzer's sultams[12] have been employed extensively in the synthesis of bioactive compounds. Chiral auxiliaries are enantiopure molecules that are temporarily incorporated into an achiral substrate prior to the asymmetric synthetic pathway in order to control the diastereoselectivity of the reaction and then removed to afford the required enantiomer. For this reason they should be easily attached to the substrate, removed without racemisation of the newly-created stereogenic center(s), and be separable from the cleaved product after the desired bound-construction has been achieved.

Asymmetric catalysis is one the most important and widely used methods to directly furnish a broad range of molecules in enantiomerically pure form and quantitative yield. A chiral catalyst[13,14] promotes the conversion of prochiral molecule to the chiral product with a preference for one enantiomer. Since the interaction between the catalyst and the substrate is reversible, the catalyst is not consumed during the process and can be introduced in a new catalytic cycle, minimising the cost and the waste generated. Catalysts are generally categorised as being either metal-based, enzymatic or, the more recently popularised, organocatalysts.

Biocatalysis utilises enzymes or live microbial culture to accelerate specific reactions.[15] Due to their complex three-dimensional structure, biocatalysts provide high chemo-, regio-, diastereo- and enantioselectivity in a large range of processes. Such high selectivity is potentially useful in chemical synthesis as it may provide several benefits, such as reduced use of or avoidance of protecting groups, minimised rates of side reactions, easier separation, and lower environmental impact. However, this strategy suffers from some drawbacks in terms of the availability of biocatalysts in both enantiomeric forms, limitations with regard to substrate scope, and use of mild conditions to avoid the formation of side products.[16]

Organometallic catalysis has been employed in a wide variety of oxidations, reductions and reactions catalysed by Lewis acids.[17] The success of this technology is due to the affinity of metals for chiral ligands to form metal-organic ligand complexes which are involved in asymmetric induction.

An important contribution to this field was made in 1970, when following Wilkinson's work on the catalytic hydrogenation with triphenylphosphine complexes of rhodium chloride, Knowles[18] at Monsanto developed an industrial process for the enantioselective synthesis of the anti-Parkinson drug, L-Dopa **9** (Scheme 1.2). They demonstrated that rhodium-chiral phosphine complex (*R*,*R*-DIPAMP)[19] was able to catalyse the hydrogenation of the prochiral olefinic substrate **7**, generating a chiral center **8** with high enantioselectivity. In recognition of his achievement, Knowles shared the 2001 Nobel Prize in chemistry with Ryoji Noyori, for their work on asymmetric catalytic hydrogenation, and with K. Barry Sharpless[20] for his work on asymmetric catalytic oxidation.



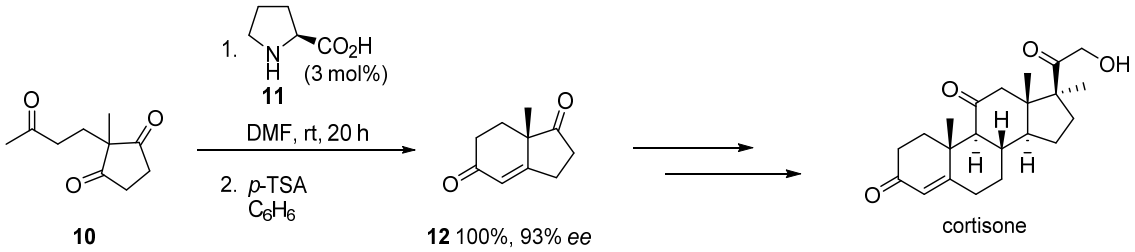
Scheme 1.2 The Monsanto synthesis of L-DOPA using asymmetric catalytic hydrogenation.

1.1.1 Organocatalysis: a historical perspective

In the last decade, the use of small chiral organic molecules as catalysts has emerged as a valid alternative to metal-ion catalysis[21] and as a powerful method of stereoselective synthesis.

Organocatalysis is described as the acceleration of the rate of an organic reaction induced by the addition of a substoichiometric amount of a low-molecular weight organic compound. Many of the catalysts used are inexpensive to prepare and readily available from natural sources as single enantiomers (*e.g.* proline, cinchona alkaloids). They are usually non-toxic, environmentally friendly and more stable than enzymes or other bioorganic catalysts. Because of their general insensitivity to air and moisture,[22] in comparison to many metal-based complexes, the execution of these reactions does not usually require special conditions such as an inert atmosphere or the use of anhydrous solvents and/or reagents.

A remarkable breakthrough in organocatalysis came about in the early 1970s, when Eder, Sauer and Wiechert,[23] together with Hajos and Parrish,[24] found that L-proline **11** catalyses the aldol cyclisation of triketone **10** in a highly enantioselective fashion. This discovery has long been recognised as one of the earliest examples of asymmetric catalysis applied to synthetic organic chemistry. As shown in Scheme 1.3, chiral enedione **12** was obtained in high yield and excellent enantiomeric excess, and was shown to be a useful intermediate in the total synthesis of steroids.



Scheme 1.3 The Hajos-Parrish-Eder-Sauer-Wiechert reaction.

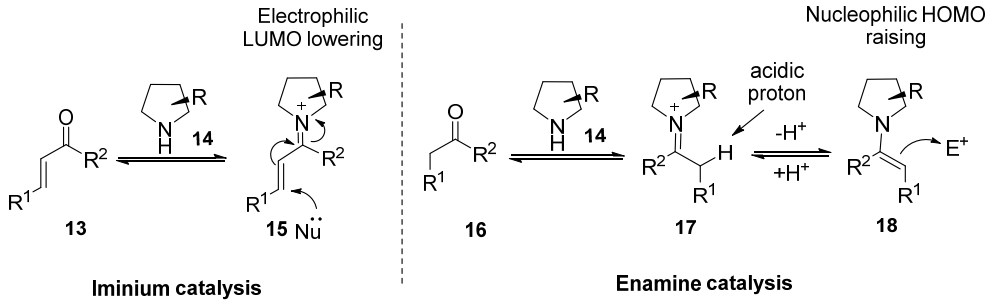
In the late 1990s, Yang,[25] Shi,[26] Denmark,[27] Miller,[28] Jacobsen,[29] Corey[30] and their respective co-workers showed for the first time that organocatalysis can be adapted to multiple reaction types and used to address some common challenges in asymmetric synthesis. Shortly after, work on enamine catalysis undertaken by Carlos Barbas, Richard

Lerner and Benjamin List,[31] followed by MacMillan[32] and co-workers'studies on iminium ion catalysis demonstrated that small molecules could catalyse the same chemical reactions as enzymes by similar mechanisms. Since then, interest in organocatalysis has peaked, making way for an intense period of research into the elucidation of generic modes of catalyst activation, induction and reactivity.

1.1.2 Advent of generic modes of action in organocatalysis

The two most popular organocatalytic activation modes to date are identified: iminium ion and enamine based catalysis.[31,32] Both are based on the formation of reactive species arising from reversible interactions, in a highly organised transition state, between a chiral catalyst and a functional group of the substrate.

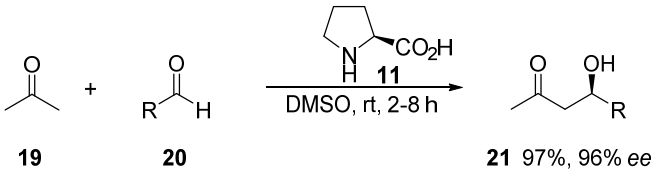
Iminium ion catalysis involves the activation of an *α*,*β*-unsaturated carbonyl moiety (**13**) by an amine catalyst such as **14** *via* reversible generation of an iminium ion intermediate **15**, which results in a lowering of the energetic potential of the lowest unoccupied molecular orbital (LUMO) (Scheme 1.4).[33,34] As a consequence, the carbonyl group is more activated towards nucleophilic addition such as Knoevenagel[35] condensation and Michael additions.[36] With respect to a system such as **16**, the formation of the iminium salt increases the acidity of the *α*-proton (**17**), which facilitates tautomerisation to the enamine intermediate **18**. In this case, the resulting activated species presents a higher energy occupied molecular orbital (HOMO), which promotes the reaction of the substrate with electrophiles (Scheme 1.4).[31,32]



Scheme 1.4 Carbonyl activation *via* iminium and enamine based catalysis.

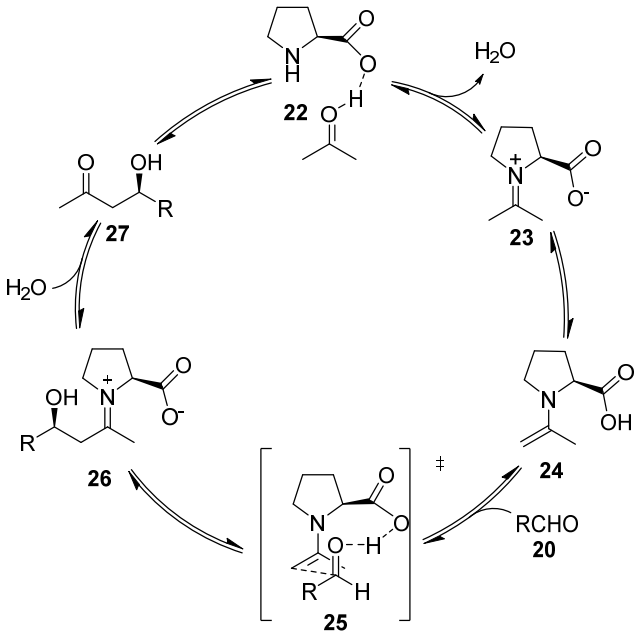
Although the aforementioned Hajos-Parrish-Eder-Sauer-Wiechert reaction[24] was widely appreciated for its fundamental and practical significance, a precise understanding of a mechanism had remained elusive for years, until recently. Theoretical and experimental

investigations carried out by List *et al.*[31] have provided a rational basis for proline's mode of action. The authors reported the first study on the amine-catalysed asymmetric intermolecular aldol reaction (Scheme 1.5).[31] They found the reaction between aldehyde **20** and an excess of acetone **19** proceeded in the presence of a catalytic amount of (*S*)-proline **11** (20-30 mol%) in DMSO, to give the desired product **21** in good yield and enantioselectivity (Scheme 1.5).[31]



Scheme1.5 Proline-catalysed direct asymmetric intermolecular aldol reaction.

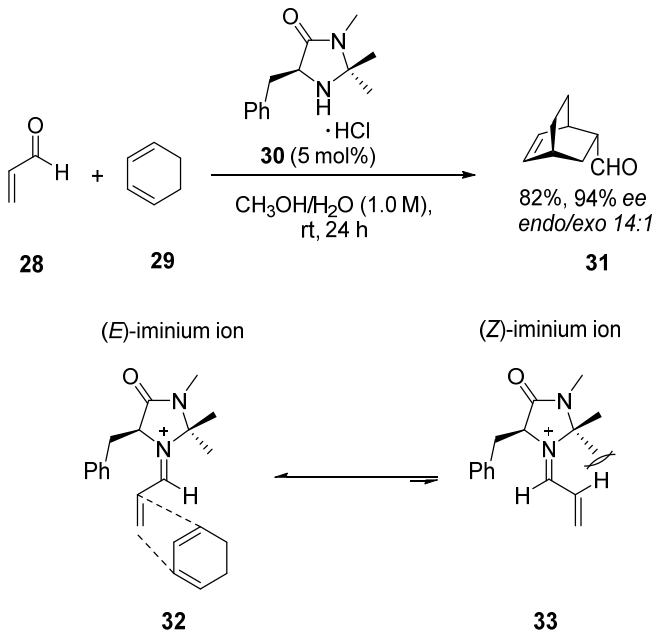
The reaction involves the formation of an enamine intermediate, similarly to the mechanism proposed for class I aldolases.[37,38] Initially, (*S*)-proline acts as a general Brønsted acid co-catalyst, by activating the carbonyl groups towards nucleophilic attack by the amine moiety (**22**). Subsequent loss of water leads to the formation of the iminium species **23**, which after deprotonation by the carboxylate of (*S*)-proline, provides **24**. At this stage, enamine **24** attacks aldehyde **20** *via* the highly organised pre-transition state assembly (**25**) to furnish **26**.



Scheme 1.6 Proposed mechanism of the proline-catalysed intermolecular aldol reaction.

Within the transition state, protonation of the H-bond acceptor occurs by the acid functionality of the (*S*)-proline, which is *anti* with respect to the enamine double bond. This rationalises the stereochemistry of the aldol reaction product **27**, which is released along with the catalyst during the hydrolysis step (Scheme 1.6).

Shortly after, MacMillan and co-workers described the first organocatalytic Diels-Alder reaction between dienes and *α,β*-unsaturated aldehydes, the chiral imidazolidinone catalyst **30** was found to activate dienophile **28** to react with **29** *via* an iminium ion intermediate (Scheme 1.7),[32] furnishing the cyclic *endo* and *exo* adducts **31** (in a ratio 14:1) in good yield and excellent enantiomeric excess.



Scheme 1.7 Enantioselective Diels-Alder reaction *via* iminium ion intermediate.

Computational models revealed the *E* iminium ion **32** to be conformationally favoured over the corresponding *Z* intermediate **33**, in which the *α*-hydrogen atom resides on the same side as the geminal methyl groups in the catalyst, thereby reducing unfavourable steric interactions (Scheme 1.7). In addition, the benzyl group sterically blocks the 'top' face, which facilitates the approach of the diene to the *si* face of the intermediate.[32,39,40]

Another activation mode widely explored in organocatalysis employs small chiral molecules bearing hydrogen-bond donor moieties.[41,42] By analogy to classical Lewis acids, these catalysts activate Lewis bases such as carbonyl groups, *via* H-bonding interactions (general acid catalysis), rendering them more reactive towards nucleophilic

species. In particular, hydrogen bonding can effectively stabilise a developing negative charge on the oxygen heteroatom within a transition state of the rate determining addition step, bringing about LUMO lowering activation and accelerated reaction rates.

1.2 Hydrogen bonding catalysis mediated by (thio)ureas

Hydrogen bonding is one of the most common molecular recognition and activation mechanisms exploited by enzymes and antibodies in living organisms for the promotion of various biological transformations (*e.g.* amide hydrolysis catalysed by serine proteases).[43] Pioneering studies conducted by Hine *et al.,* demonstrated the catalytic ability of 1,8-biphenylenediol (**34**, Figure 1.1) in the aminolysis of epoxides, and proposed that the increased reactivity observed resulted from the simultaneous formation of two strong hydrogen bonds to the same oxygen atom of the electrophile.[44]

This theory was further developed by Kelly *et al.,*[45] who showed that biphenyldiol (**35**, Figure 1.1) bearing electron-withdrawing substituents at the *para*-positions, was capable of promoting the Diels-Alder reaction by establishing a double hydrogen bond interaction with the dienophile. Later, Etter and co-workers reported that *N*,*N'*-diarylureas with electron-withdrawing groups (EWG) in the *meta* positions (**36**, Figure 1.1) can form hydrogen bonds with a wide number of Lewis base molecules (such as nitroaromatics, ethers, ketones and sulfoxides)[46,47] by co-crystallisation. This work along with the previously mentioned studies inspired the design of many more diaryl(thio)ureas organocatalysts.[48]

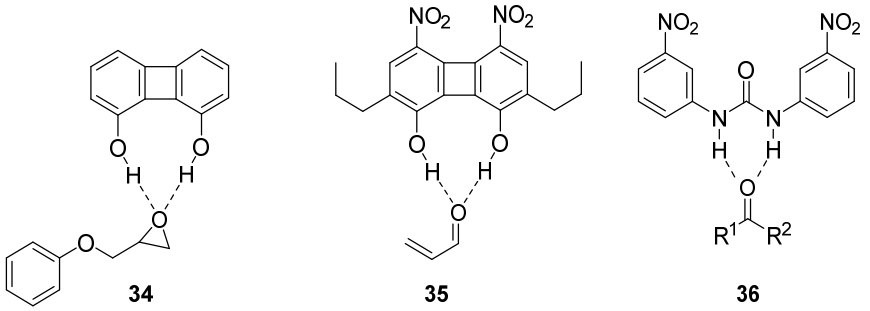
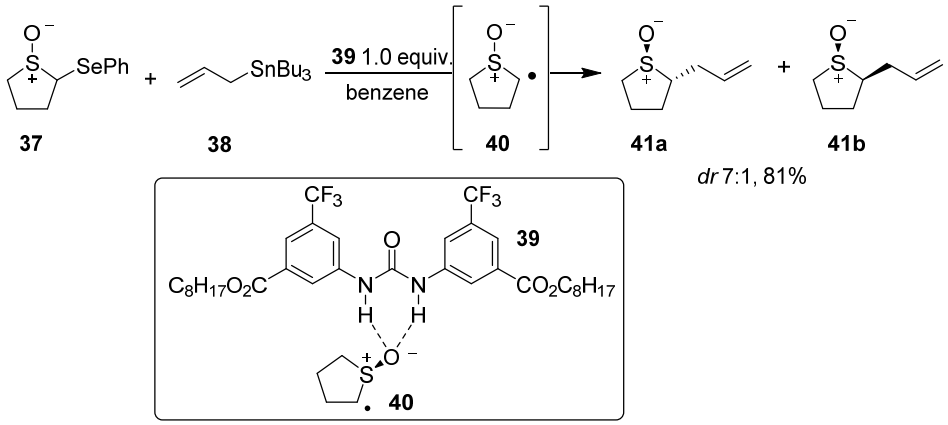


Figure 1.1 Models of double hydrogen bond donation developed by Kelly, Etter.

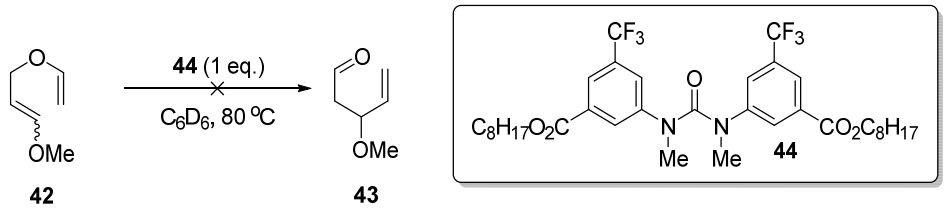
The application of (thio)urea in general acid-catalysed reactions was first reported by Curran and co-workers.[48] They demonstrated the ability of diarylurea **39**, bearing EWGs

and a lipophilic octyl ester in each phenyl ring to act as a powerful H-bond donor in the allylation of cyclic sulfinyl radicals (**37**, Scheme 1.8). This study showed stoichiometric amounts of **39** to promote the reaction in higher yield and diastereoselectivity than when other strong Lewis acids were employed – furnishing **41a,b** in a *trans*:*cis* ratio of 7:1.



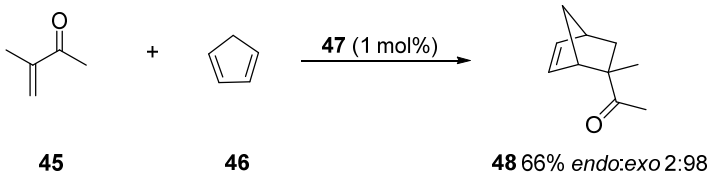
Scheme 1.8 Allylation of cyclic sulfinyl radicals promoted by catalyst **39**.

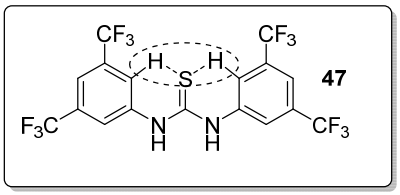
The same catalyst (**39**) was later found to accelerate the rate of the Claisen rearrangement of **42** to **43** up to 22-fold when used in stoichiometric amounts. Further evidence for Hine's hydrogen bonding activation model arose when **44**, devoid of hydrogen bond donors, failed to promote the reaction (Scheme 1.9).[49]



Scheme 1.9 Claisen rearrangement catalysed by diaryl(thio)urea catalysts.

Some time later, inspired by Curran's findings, Schreiner *et al.*[50] reported the ability of thiourea **47** to catalyse the Diels-Alder cycloaddition between cyclopentadiene (**46**) and methacrolein **45**, affording **48** as a mixture of *endo* and *exo* products - exhibiting a complementary mode of action to strong Lewis acids such as $AlCl_3$ and $TiCl_4$[51] (Scheme 1.10). Among the various thiourea analogues under investigation, catalyst **47** was found to satisfy the steric and electronic requirements for optimal catalytic efficiency, along with a range of other desirable properties.





Scheme 1.10 Diels-Alder reaction catalysed by diaryl(thio)urea catalyst **47**.

Firstly, thioureas generally possess greater solubility in a range of organic solvents, and the lower electronegativity of sulfur makes self-association far more limited compared to the corresponding urea derivatives. Moreover, the higher acidity of N-H protons due to the presence of a sulfur heteroatom and extra trifluoromethyl group on the aromatic ring increases the hydrogen-bond donating power of thiourea derivatives.

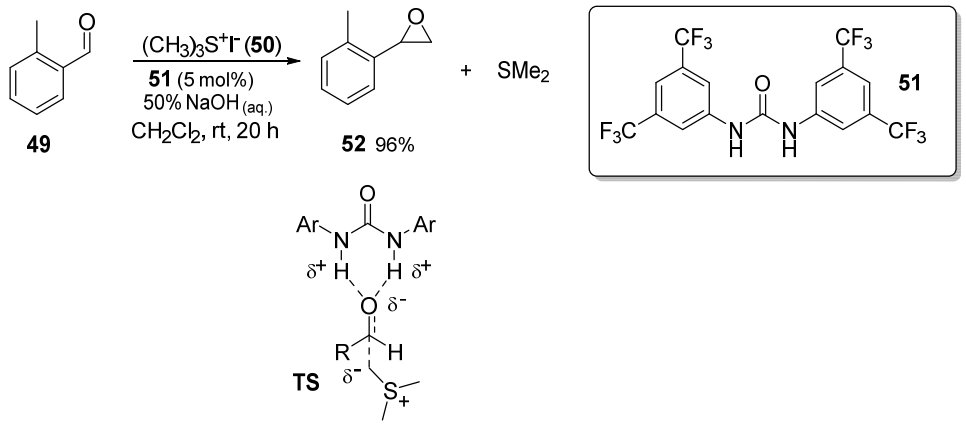
In addition, computational studies have underlined that the installation of electron-withdrawing substituents (such as -CF_3) in *meta*-positions rigidifies the polar interactions between hydrogen atoms with the Lewis-basic sulfur atom (see Scheme 1.10), which increases the energetic rotational barrier of the catalyst, minimising entropy loss upon binding with the substrate.[51]

These pivotal works had the merit to highlight the huge potential of diaryl(thio)ureas as hydrogen bond donors, turning researchers' attention towards the extension of catalyst scope with respect to a variety of chemical transformations - a number of which will be discussed below.

In 2003, Takemoto[52] and co-workers described the nucleophilic addition of trimethylsilyl cyanide to nitrones mediated by a variety of thiourea catalysts. In line with Schreiner's study, the high yield and the acceleration of the rate of reactions were achieved by efficient H-bonding between the catalyst and nitrones.

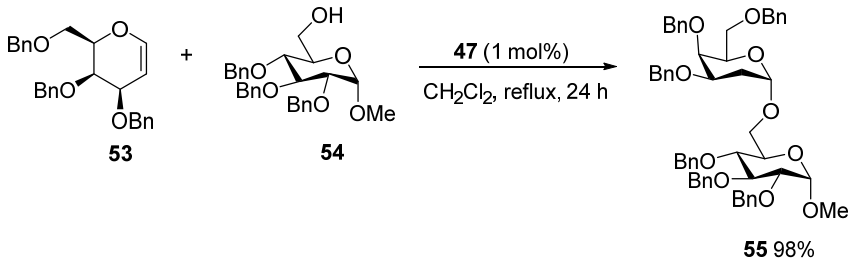
More recently, our group has shown for first time that the *N*,*N*′-diarylurea **51** can efficiently catalyse the sulfonium ylide-mediated (**50**) epoxidation reaction of aromatic aldehydes[53] such as 2-methylbenzaldehyde (**49**) (Johnson-Corey-Chaykovsky reaction),[54]

to afford the corresponding product **52** in high yield. As a rationale of this outcome it was postulated that within the transition state, hydrogen bond donation by the catalyst stabilised the arising negative charge on the oxygen heteroatom during the addition of the ylide to the aldehyde -the rate-determining step (Scheme 1.11).



Scheme 1.11 Diarylurea (**51**) promoted Corey-Chaykovsky reaction.

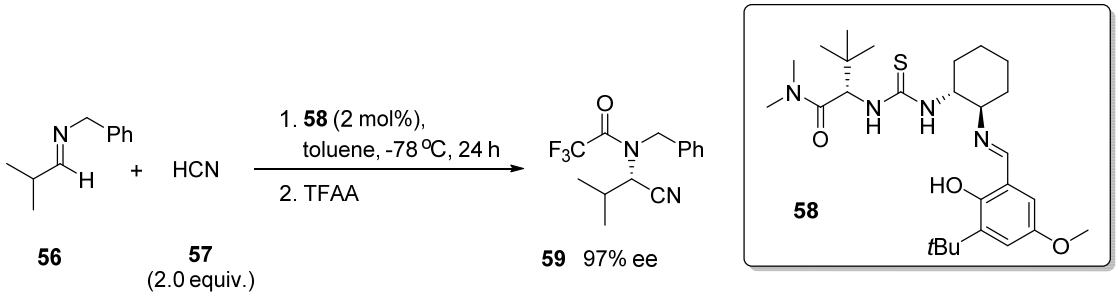
In 2015, inspired by Schreiner's report[55] on the use of catalyst **47** to promote the protection of alcohols with dihydropyran (DHP), McGarrigle *et al*. reported an efficient catalytic glycosylation of galactals (*e.g.* **54**) with a wide range of glycosyl acceptors such as **53** (Scheme 1.12).[56] This reaction proceeds with excellent yield and high selectivity for the *α*-anomer (*e.g.* **55**), and is well tolerated by most commonly used alcohol protecting groups such as benzyl, silyl ethers, benzoyl esters, and acetals. The versatility of this process was highlighted by its successful application in a one-pot stereoselective synthesis of a trisaccharide.



Scheme 1.12 Glycosylation of galactals mediate by thiourea **47**.

1.2.1 Chiral (thio)urea organocatalysts

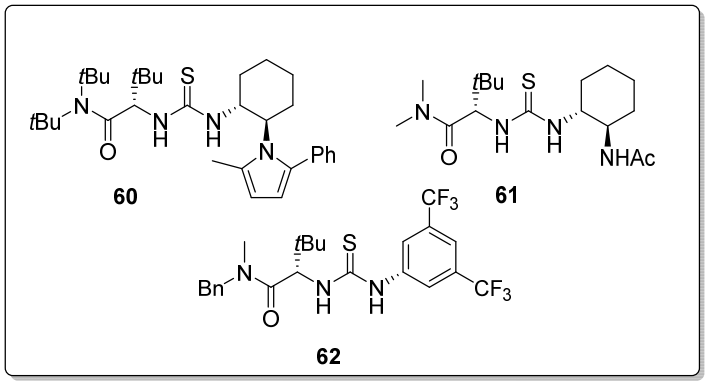
During studies on the evaluation and design of ligands for the metal-catalysed version of the asymmetric Stecker reaction, Jacobsen *et al.* observed that one of the (thio)urea-derived ligands screened was unexpectedly able, in absence of metal additives, to furnish the desired product with a higher degree of enantiocontrol.[57] Further optimisation from a parallel synthetic library led to the identification of Schiff-base thiourea **58** as an efficient catalyst for the highly enantioselective synthesis of Strecker adducts **59** by the addition of HCN (**57**) to aromatic *N*-benzyl aldimines **56** (Scheme 1.13).



Scheme 1.13 Asymmetric Strecker reaction catalysed by Schiff base catalysis.

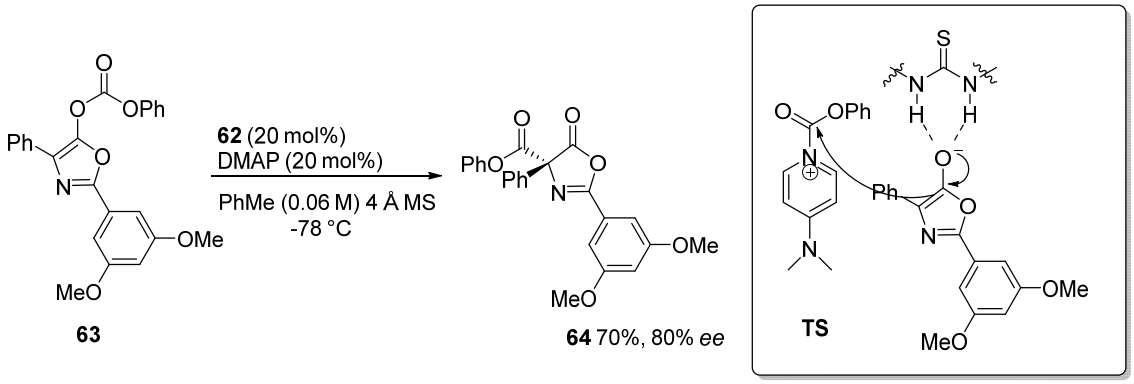
According to computational and mechanistic studies, thiourea catalyst **58** binds to the (*Z)* isomer of the imine preferentially *via* double hydrogen-bond donation to the nitrogen lone pair in order to minimise unfavourable steric interactions between the catalyst and the large imine substituents. This interaction activates the substrate in a chiral environment and directs the addition of HCN over the diaminocyclohexane moiety of the catalyst and away from the amino acid/amide side.[57]

In the following years, the versatility of this new type of chiral thiourea organocatalyst was investigated by Jacobsen's group in a variety of stereoselective processes such as Mannich reactions,[58] imine hydrophosphonylations,[59] acyl-Pictet-Spengler reactions[60] and Baylis-Hillman reactions.[61] Interesting to note was the discovery that some of these transformations could be catalysed by simpler derivatives of **58** such as **60**, **61** and **62** (Scheme 1.14) in which the Schiff base moiety was removed from the main framework, without compromising enantioselectivity.



Scheme 1.14 Simplified chiral (thio)urea catalysts.

Inspired by these findings, in 2011 Seidel *et al.* developed an asymmetric Steglich rearrangement of *O*-acylated azlactones (*e.g.* **63**) to *C*-acylated products (*e.g* **64**), promoted by catalyst **62** in combination with DMAP.[62]



Scheme 1.15 Asymmetric Steglich rearrangement catalysed by **62**.

Seidel's proposed mechanism for this reaction states that catalyst **62** initially activates the azalactone towards nucleophilic attack by DMAP *via* hydrogen bonding with the carbonyl group of **63**. The azlactone anion generated is then stabilised by hydrogen-bond donation from the thiourea moiety, followed by nucleophilic addition to the acylpyridinium cation (Scheme 1.15).[62]

1.2.2 Chiral bifunctional thioureas in organocatalysis

Although chiral thiourea derivatives have demonstrated their potential as general acids in several types of enantioselective reactions, their application is somewhat limited with respect to substrate scope. In order to overcome this limitation a nucleophilic Lewis basic moiety was incorporated into the catalyst structure making dual activation of the electrophile and nucleophile possible (*via* a similar mode of action to natural enzymatic

systems, Figure 1.2). These systems can be adapted to asymmetric reactions involving various electron-deficient substrates, whilst guaranteeing excellent reaction rates and high levels of stereocontrol over the addition step. The two main structural features of the majority of these novel organocatalysts are represented by the presence of a tunable aromatic moiety connected to one thiourea nitrogen atom, which effects the catalyst's rigidity and the hydrogen-bond donor's proficiency, and at the other a chiral Brønsted base functionality.

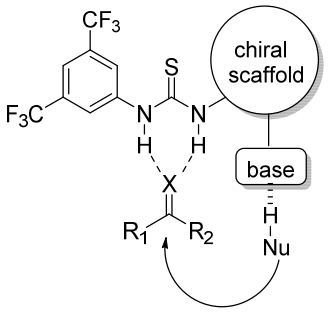
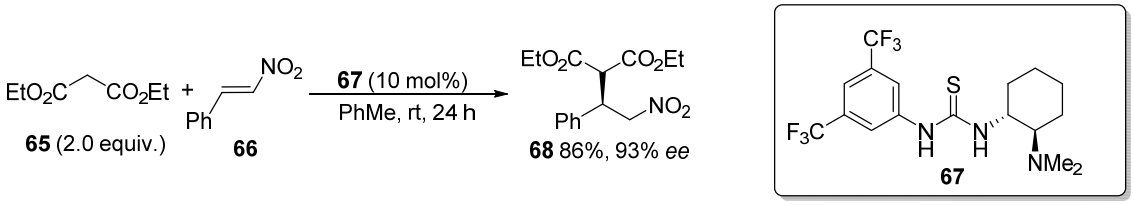


Figure 1.2 Design of bifunctional thioureas.

The first thiourea-based bifunctional catalyst was designed in 2003 by Takemoto *et al*., who replaced one of the aryl rings of Schreiner's diaryl thiourea with a cyclic-(*N*,*N*-dimethylamino) hexane as a chiral scaffold (*e.g.* **67**, Scheme 1.16).[63] They then demonstrated that a catalytic amount of **67** could promote the Michael type addition of diethyl malonate **65** to *β*-nitrostyrene **66**, forming **68** in excellent *ee* under optimised conditions (Scheme 1.16).[63]



Scheme 1.16 Takemoto's bifunctional thiourea catalyst **67** promoting Michael addition.

In order to rationalise the stereoinduction observed, a mechanism and transition state model was proposed. As shown in Figure 1.3, the tertiary amine is responsible for deprotonation of the diethyl malonate and consequent formation of a highly nucleophilic enolate species which attacks one face of the nitroolefin, which is activated by dual hydrogen-bond donation from the thiourea moiety.[64]

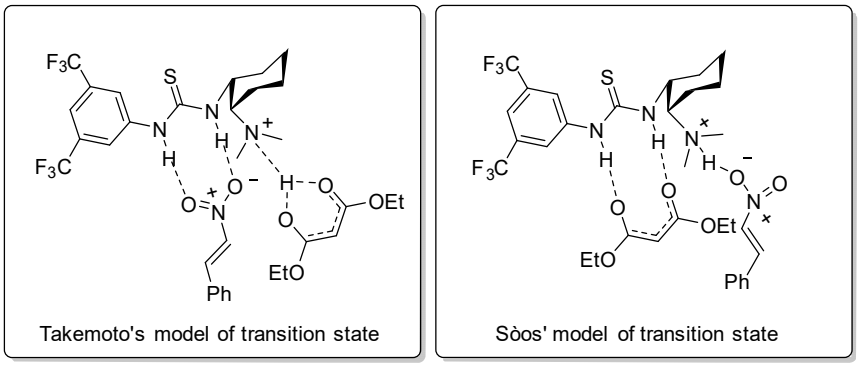
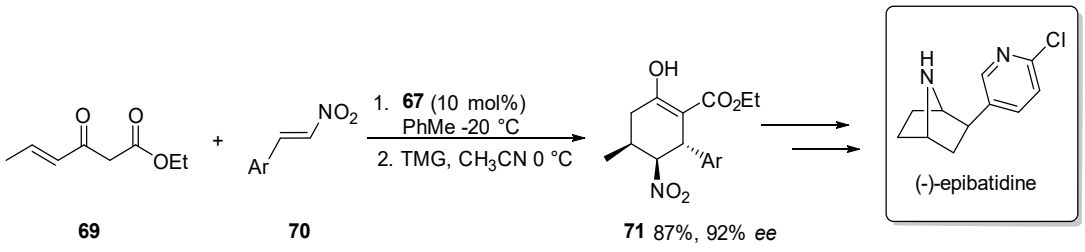


Figure 1.3 Transition state models proposed by Takemoto (left) and Sòos (right).

However, later an alternative mechanism was postulated by Soòs *et al*.,[65] in which the carbonyl groups of the deprotonated malonate ester interact with the N-H groups of the thiourea and activation of the nitroolefin occurs *via* interaction with the protonated amino group (Figure 1.3). Both mechanisms claimed that in order to achieve high yield and selectivity, the thiourea moiety and tertiary amino group must be present on the same chiral scaffold.

The catalytic activity of **67** was also evaluated with a range of 1,3-dicarbonyl substrates such as *γ*,*δ*-unsaturated *β*-ketoesters (**69**), which were shown to be compatible in Michael additions with nitrolefins **70**, (Scheme 1.17). This reaction has shown great potential for its synthetic utility in the preparation of chiral cyclohexanones (*e.g*. enol **71**), one having being used as a precursor in the stereoselective total synthesis of (-)-epibatidine, a potent nicotinic acetylcholine receptor agonist.[66]

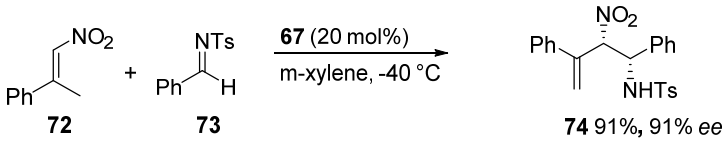


Scheme 1.17 Bifunctional thiourea-catalysed Michael addition of 1,3-dicarbonyl compounds to nitroolefins.

Based on these pioneering works, the synthetic potential of chiral thiourea-amine organocatalysts and their derivatives were explored rigorously by several groups in a

broad range of transformations, such as asymmetric Mannich reactions,[67] Henry reactions[68] and thio-Michael cyclisations.[69]

A noteworthy application of Takemoto's catalyst was reported in 2009 by Xu and co-workers, who developed the asymmetric Morita-Baylis-Hillman reaction of nitroalkene **72** to *N*-tosylimine **73** promoted by catalyst **67** (Scheme 1.18).[70] This transformation renders easy access to *β*-nitro-*γ*-enamines such as **74**, which are valuble intermediates in the synthesis of biologically active compounds, in high diastereo- and enantioselectivities.



Scheme 1.18 Asymmetric Morita-Baylis-Hillman reaction mediated by catalyst **67**.

1.2.3 Chiral bifunctional organocatalysts containing squaramides moieties

Over the past several years, chiral (thio)urea derivatives[71] have largely dominated the general acid/base bifunctional asymmetric catalysis,[72] proving their capability as powerful hydrogen-bond donors in a wide array of useful enantioselective processes. However, more recently, among the pool of H-bond donor groups, squaramides have emerged as a valid alternative to the highly efficient (thio)urea-based systems due to their peculiar physical and structural features, which form the basis of their rise in popularity.[73]

Squaramides were first synthesised in 1966,[74] starting from squaric acid. Since then, intense research has been carried out into understanding their particular H-bonding ability and distinguishing their main structural differences[75] from (thio)urea analogues.

Squaramides are four membered ring systems possessing duality in hydrogen-bonding and have the capacity to form up to three hydrogen-bonds.[73,75] The two N-H moieties can act as hydrogen-bond donors to anionic species, while the two carbonyl functionalities can be engaged in cationic recognition and as hydrogen bond acceptors (Figure 1.4). Squaramides are considered a vinylogous amide with a rigid structure as both nitrogen lone pairs can be delocalised through the carbon-oxygen double bound (Figure 1.4),[73,75] generating a cyclobutenediolate system with two positive charges, bearing aromatic character according to Hückel's rules (*e.g.* 4n + 2, n = 0). Consequently, more rotational

restrictions around C-N bonds are observed in squaramide structures than in (thio)ureas, which cause both carbonyl and amine groups to be coplanar.[76]

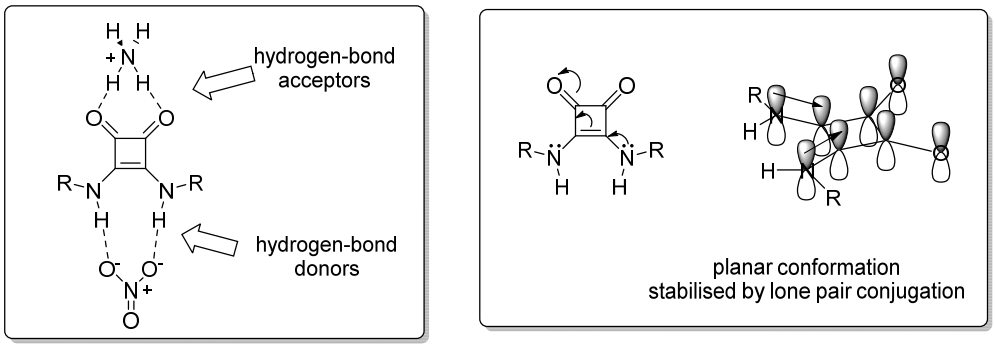


Figure 1.4 Dual hydrogen-bonding and resonance structures of squaramides.

While hydrogen-bond duality allows for binding to a broad range of substrates, the rigidity reduces entropy loss on substrate binding. Another significant difference between thioureas and squaramides is the relative distance and spacing between the two N-H groups. According to some calculations conducted by the Takemoto and Rawal groups, the distances for *N*,*N*'-dimethylthiourea and *N*,*N*'-dimethylsquaramide were found to be approximately 2.13 Å and 2.72 Å respectively.[73]

Moreover, the square structure of the cyclobutenedione ring also induces a convergent orientation (6°) of the N-H groups (Figure 1.5), a property not found in thioureas, which confers to these molecules different binding properties during the transition state (Figure 1.5).[75]

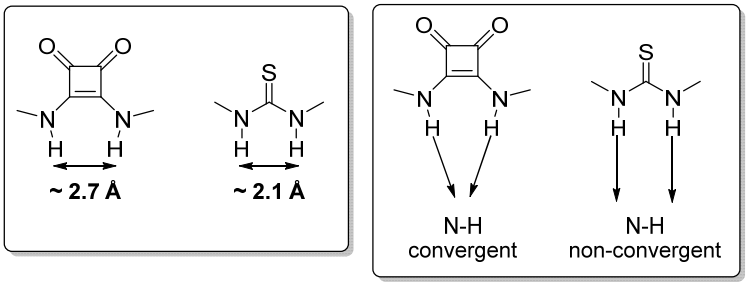
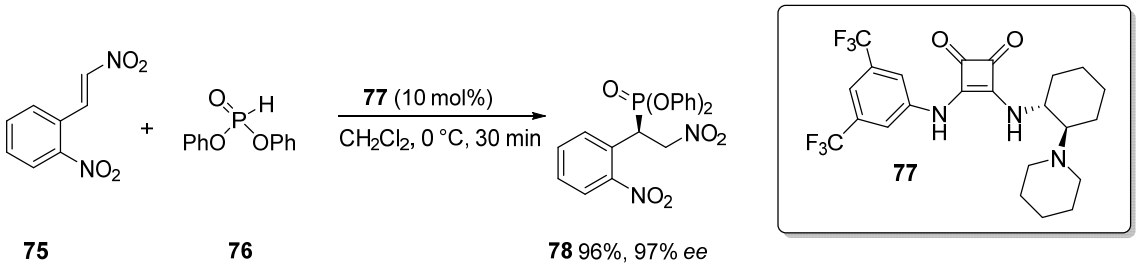


Figure 1.5 Difference in H-bond spacing distances and H-bond orientation between squaramides and thioureas.

Based on this information, in 2010 Rawal *et al.* [77] developed a bifunctional catalyst (**77**) containing a squaramide moiety and a chiral amine, which successfully catalysed the conjugate addition of diphenylphosphite (**76**) to nitroalkene **75**. The nitrophosphonate **78**,

which is a precursor to biologically active β-amino phosphonic acids, was obtained in excellent yield and enantioselectivities (Scheme 1.19).[77]



Scheme 1.19 Michael addition promoted by bifunctional squaramide catalyst.

The utility of catalyst **77** was not confined to the reaction illustrated in Scheme 1.19, but also extended to other types of transformations such as enantioselective Friedel-Crafts[78] reactions and the α-amination of 1,3 dicarbonyl compounds.[79] Furthermore, inspired by Rawal's studies, squaramides structurally similar to **77** and new squaramide-based H-bonding catalysts have been designed for several other applications.[80,81,82]

1.3 Cinchona alkaloids as bifunctional organocatalysts

Cinchona alkaloids are abundant natural products present in the bark of South-American trees of the genus *Cinchona*.[83] Renowned for their antimalarial properties, they were introduced to the European market in the seventeenth century, and have since played a pivotal role in the field of medicine, having emerged as effective anticancer and analgesic agents.[84] The four main alkaloids isolated are quinine (**79**), cinchonidine (**80**) and their *pseudo*enantiomers quinidine (**81**) and cinchonine (**82**), which are considered 'privileged'[85] chirality inducers in the area of asymmetric catalysis.[86] They possess relatively rigid structures in which the bulky basic quinuclidine and Brønsted acidic hydroxy functionality at the C-9 position are in close proximity to one another within a defined chiral environment.

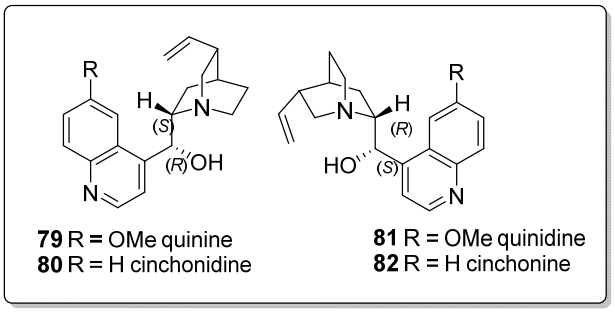
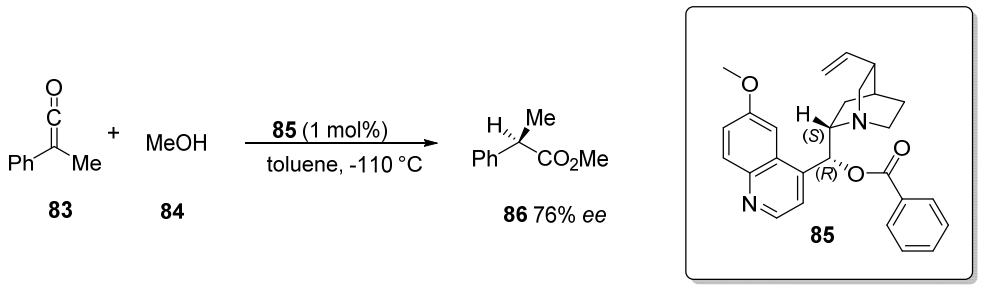


Figure 1.6 Structures of catalytically important cinchona alkaloids.

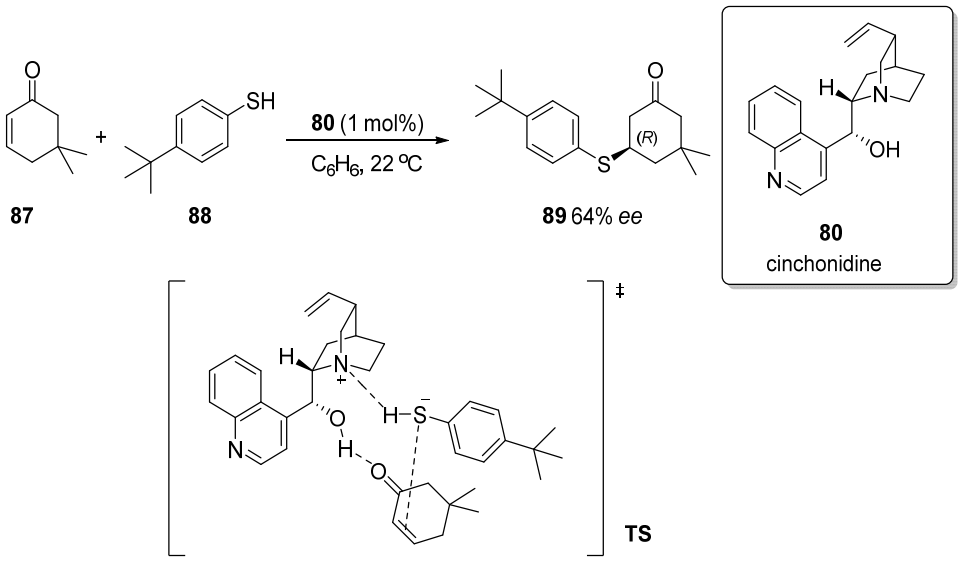
The first use of cinchona alkaloids dates back to 1853, when Pasteur[87] used them as resolving agents for the separation of a racemic mixture of tartaric acid. Besides classical resolution methods, the most interesting application of cinchona alkaloids in synthetic chemistry resides in their ability to promote enantioselective transformations. The first asymmetric reaction carried out using cinchona alkaloids was the addition of HCN to benzaldehyde, described in 1912 by Breding and Fiske.[88] Although the enantioselectivities achieved were low for this transformation (~10% *ee*), this work had the merit of exemplifing the possibility of obtaining enantioenriched products of opposite chirality when performed using either quinine or its *pseudo*enantiomer quinidine. Pracejus was the first to obtain useful levels of enantioselectivity when he employed *O*-acetylquinine (**85**) as a catalyst in the reaction between methanol **84** and phenylmethylketene **83**, affording (-)-*α*-phenylmethylpropionate (**86**) in 76% *ee* (Scheme 1.20).[89]



Scheme 1.20 Pracejus' enantioselective synthesis of (-)-*α*-phenylmethylpropionate.

Inspired by this seminal work, Wynberg and co-workers[90] embarked on a series of studies into the use of various cinchona alkaloids as Lewis-basic/nucleophilic catalysts in asymmetric Michael additions of aromatic thiols (**88**) to conjugated cycloalkenones (**87**). They found that the presence of a free C-9 hydroxyl functionality is essential for

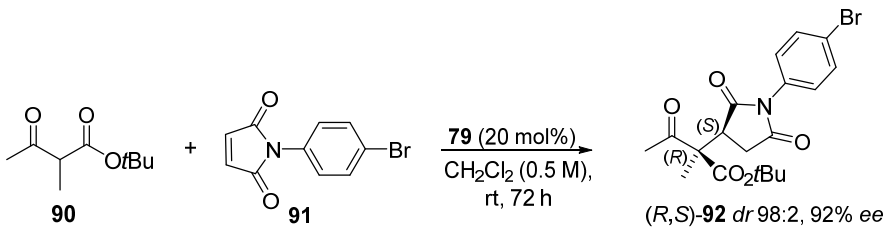
furnishing products (*e.g.* **89**) with significant levels of enantiocontrol (Scheme 1.21). Futhermore, they speculated that these alkaloids generally act as bifunctional catalysts in which the hydroxy group activates the enone by hydrogen bonding, while the chiral base moiety deprotonates the pronucleophile (thiol) in the transition state.[90]



Scheme 1.21 Enantioselective addition of thiols to cyclic enones catalysed by cinchonidine **80**.

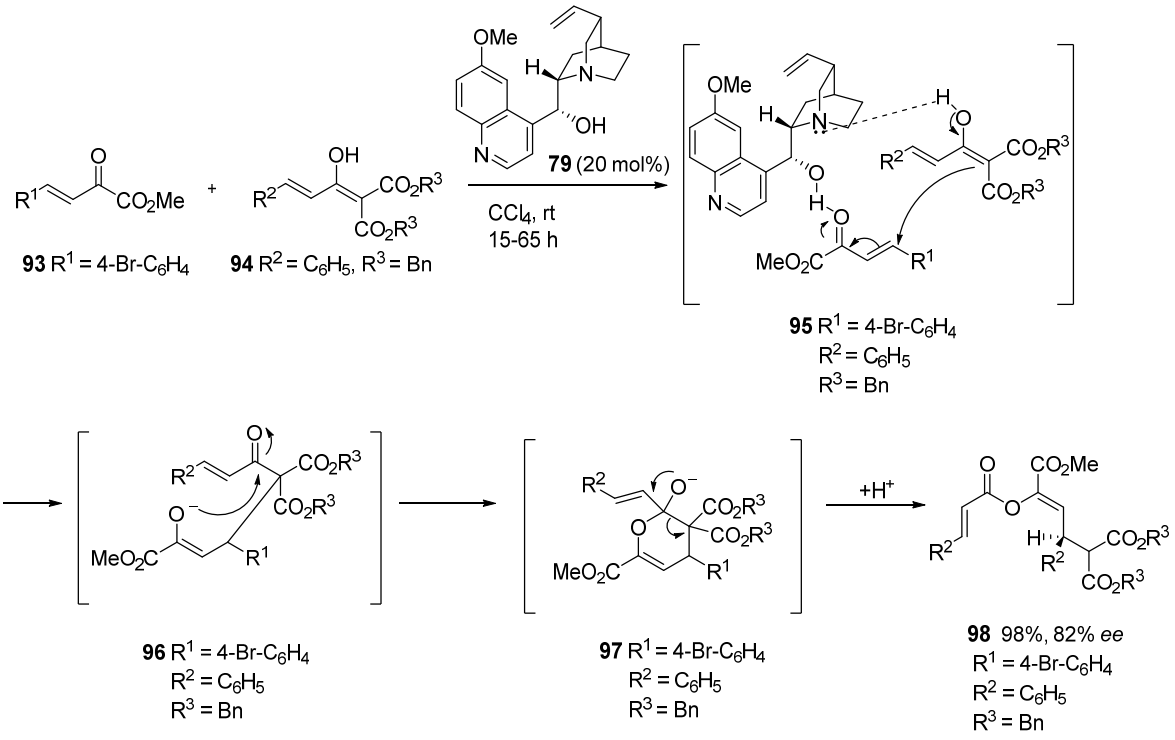
Since this discovery, the use of cinchona alkaloids has grown exponentially and much research has been directed towards investigating the versatility of *Cinchona* alkaloids on a wide range of enantioselective transformations. Selected examples of which are reported below.

In 2006, Melchiorre *et al.*[91] reported the first asymmetric Michael addition of *β*-ketoester compounds such as **90** to maleimides (*e.g.* **91**) catalysed by natural cinchona alkaloids (Scheme 1.22). The reaction promoted by quinine allowed for an one step synthesis of highly functionalised succinimide products such as **92**, bearing two contiguous stereocentres, one of which is quaternary, with very high diastereo- (*dr* up to >98:2) and enantioselectivities (up to 92% *ee*). This method is a powerful tool for the construction of quaternary stereogenic centres which normally pose a challenge to create due to steric considerations, and provides a synthetically attractive structural *motif* found in a broad range of medicinally active natural products and pharmaceutical compounds.



Scheme 1.22 Highly stereoselective Michael addition of 1,3-dicarbonyl compounds to maleimides catalysed by quinine.

Inspired by the aforementioned study by Melchiorre, Zhao and co-workers[92] investigated a double Michael addition between *β*,*γ*-unsaturated *α*-ketoesters such as **93** to malonates such as **94**, furnishing rearrangement products **98**.



Scheme 1.23 Quinine catalysed enantioselective Michael addition-oxa nucleophilic rearrangement reaction of *β*,*γ*-unsaturated *α*-keto-esters.

Various catalysts were evaluated, yet quinine was found to promote the reaction most efficiently, affording **98** in yields ranging from 68 to 98%, and enantioselectivities of up to 82% (Scheme 1.23).[92] According to the proposed mechanism the catalyst activates both electrophile and nucleophile simultaneously (**95**), leading to the formation of **96**, which then undergoes an oxanucleophilic attack to the ketone carbonyl group of **96**, generating

the intermediate **97**. Subsequent collapse of the tetrahedral intermediate followed by protonation leads to the formation of the product **98** (Scheme 1.23).[92]

1.3.1 Functionalisation of cinchona alkaloids: common modifications

Over time, several modifications to the structure of natural cinchona alkaloids have been reported in order to improve the catalysts' performance in a wider range of reactions.[84,93] There are six positions at which the structures may be modified in order to tune the catalytic activity - transformation of the alcohol at the C-9' position into another moiety being the most common. The secondary alcohol can be substituted and/or derivatised into highly valuable (thio)ureas, squaramides, amides etc., with either retention or inversion of the 'natural' absolute configurations. In addition, conversion of the 9-OH into a free amino group provides access to a class of catalysts used preferentially in enantioselective aminocatalysis, which involves the formation of enamine[31] or iminium ion intermediates[32] for the activation of nucleophiles and electrophiles respectively.

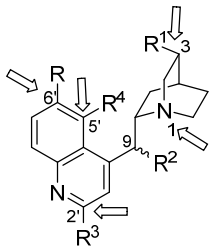


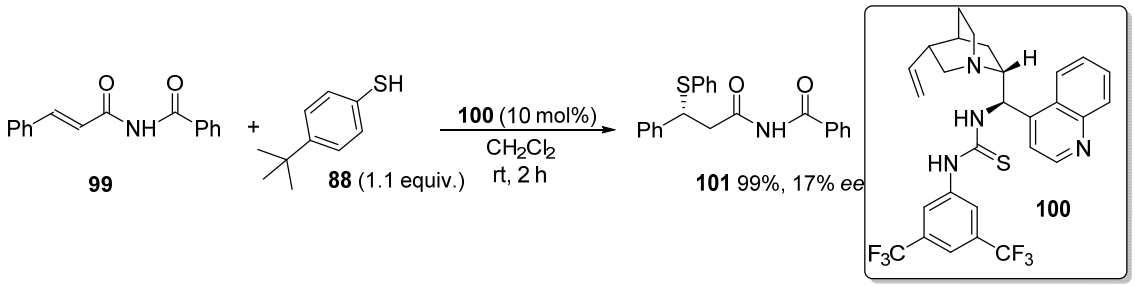
Figure 1.7 Positions most frequently modified in cinchona alkaloids.

The 6'-methoxy group of quinine and quinidine can also be readily derivatised to a phenolic free OH group, which can serve as an effective H-bond donor in asymmetric processes such as Henry reactions and Michael additions. Further fine tuning of the catalytic performance of cinchona alkaloids can be achieved by introduction of aryl or alkyl substituents at the C-2' position of the quinoline moiety. These modifications are thought to influence the steric and electronic properties of cinchona alkaloids, and can also lead to changes in the reactivity of the adjacent nitrogen atom. In the following Sections, modifications at C-9'/C-2' positions will be discussed. Aspects related to modifications at other positions will not be analysed in this thesis, however an excellent review has appeared in recent years which summarises this topic comprehensively.[84]

1.3.1.1 Thiourea moiety introduced at C-9'

Based on Takemoto's findings,[63] along with the widespread use of cinchona alkaloids in asymmetric organocatalysis, several research groups across the world designed more powerful H-bond donating cinchona alkaloid derivatives by combining the (thio)urea *motif* with a cinchona alkaloid core. This approach came with the advantages of enhancing the Brønsted acidity, rigidity and hydrogen-bond donating capacity of the natural alkaloids, which can be easily modulated by choosing appropriate substituents on the (thio)urea moiety. Additionally, this strategy allowed for access to (thio)urea derivatives of cinchona alkaloids with both 'natural' and 'unnatural' absolute configurations at C-9, leading to investigations on the effect of the stereochemistry at C-9 on the catalysts activity.

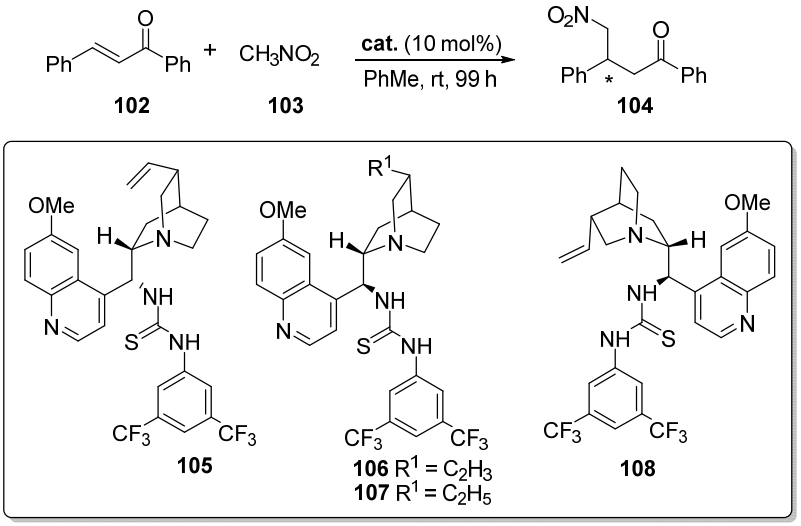
Chen and co-workers[94] were the first to probe those structures, employing thiourea-substituted cinchona alkaloids such as cinchonine **100** in the conjugate addition reaction of thiophenol (**88**) to *α,β*-unsaturated imide **99** (Scheme 1.24). Despite the high yields observed, the product **101** was isolated in low enantiomeric excess (<20% *ee*).



Scheme 1.24 The first Michael addition reaction mediated by thiourea-substituted cinchona alkaloid.

Later on, Soós *et al.*[95] developed four thiourea-substituted cinchona alkaloid catalysts, which were evaluated in the enantioselective addition of nitromethane (**103**) to (*E*)-chalcone (**102**, Scheme 1.25). Catalysts **106** and **108** were synthesised from the readily available alkaloids quinine and quinidine respectively (**79** and **81**, Figure 1.4) in two steps with overall epimerisation of the C-9 stereocentre. Unexpectedly, the thiourea derivative of quinine (**105**) with natural stereochemistry at C-9 failed to promote the reaction, just as quinine itself. Meanwhile, both *epi*-thiourea **106** and its *pseudo*enantiomer **108** proved to be active, furnishing products such as **104** with opposite absolute configurations. A

further improvement in both enantiocontrol and yield was achieved when catalyst **107**, synthesised from dihydroquinine with inversion of configuration, was employed in the same reaction under identical conditions (Scheme 1.25).

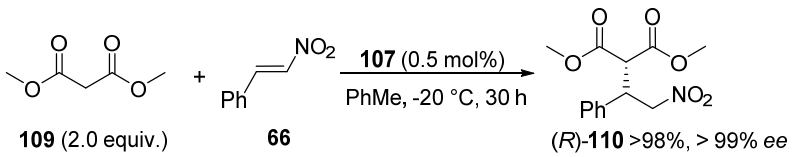


cat.	104 yield (%)	*ee* (%)
105	0%	--
106	71%	95% (*R*)
107	93%	96% (*R*)
108	59%	86% (*S*)

Scheme 1.25 Asymmetric addition of nitromethane to chalcone mediated by thiourea cinchona organocatalysts.

These results indicated that the appropriate relative stereochemistry of catalysts at C-8/C-9 is critical to obtain satisfactory levels of activity and selectivity in bifunctional catalysis.[95]

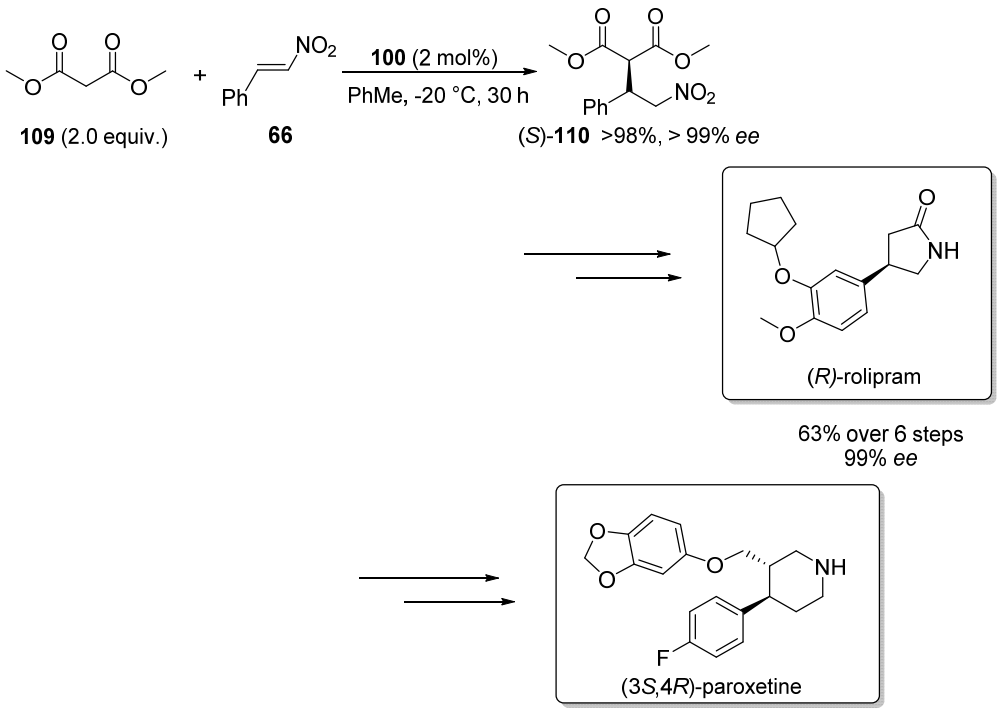
Shortly after, Connon *et al.*[96] designed a range of (thio)urea-substituted derivatives of dihydroquinine (**DHQ**) and dihydroquinidine (**DHQD**) and evaluated them in the asymmetric Michael addition of dimethylmalonate (**109**) to nitrostyrene (**66**, Scheme 1.26)



Scheme 1.26 Michael addition promoted by thiourea cinchona alkaloid catalyst **107** reported by Connon *et al*.

In particular, it was found that *epi*-dihydroquinine-derived thiourea catalyst **107** promoted the reaction at a very low loading (0.5 mol%), providing access to synthetically useful

enantioenriched nitroalkanes (*R*)-**110** in 99% enantiomeric excess and 98% isolated yield (Scheme 1.26).[96] Almost simultaneously, a similar study by Dixon *et al*.[97] investigated the use of a small library of catalysts bearing different hydrogen-bond donating moieties in the Michael addition of **109** to **66**.



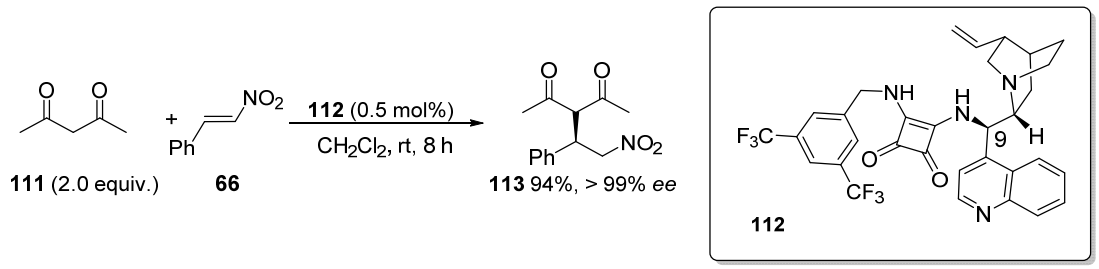
Scheme 1.27 Michael addition promoted by thiourea cinchona catalyst **100** reported by Dixon *et al*.

Of all the catalysts screened, *epi*-cinchonine-derived thiourea catalyst **100** favoured the formation of Michael adduct (*S*)-**110**, with inverted absolute configurations, albeit with yields and enantioselectivities comparable to those reported by Connon *et al*.[96] Later, Dixon *et al*. demonstrated the synthetic power of this process by employing it as the key step in both the total asymmetric synthesis of antidepressant (*R*)-rolipram and the formal total asymmetric synthesis of (3*S*,4*R*)-paroxetine (Scheme 1.27).[98]

1.3.1.2 Squaramide moiety introduced at C-9'

Since Rawal and co-workers' seminal studies on squaramides,[77] their incorporation into the cinchona alkaloid scaffold for the development of organocatalysts has gained immense popularity.

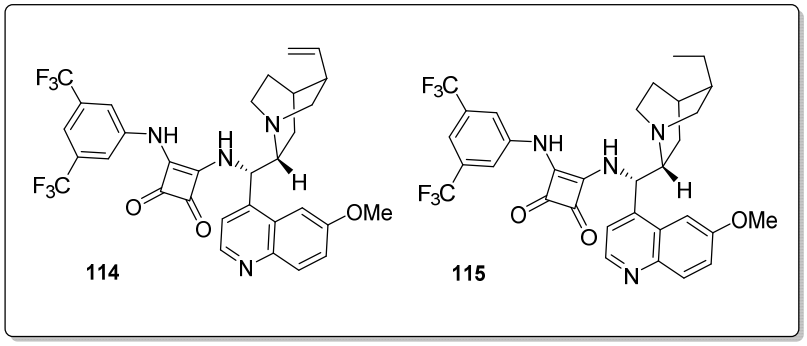
In 2008, they designed a squaramide C-9 substituted cinchona alkaloid organocatalyst **112** and evaluated it in the Michael addition between 1,3-dicarbonyl compound **111** and nitroolefin **66**, (Scheme 1.28).[99] At exceptionally low loadings (0.5 mol%), **112** was found to promote the addition smoothly, furnishing Michael adduct **113** in high yield and excellent enantioselectivity (Scheme 1.28).



Scheme 1.28 Michael addition promoted by squaramide cinchona catalyst **112**.

Afterwards, various publications emerged documenting the applications of squaramide-derived cinchona alkaloids, not only in one step C-C and carbon-heteroatom bond formations but also in various cascade reactions, which allow for rapid access to complex molecular structures.[100]

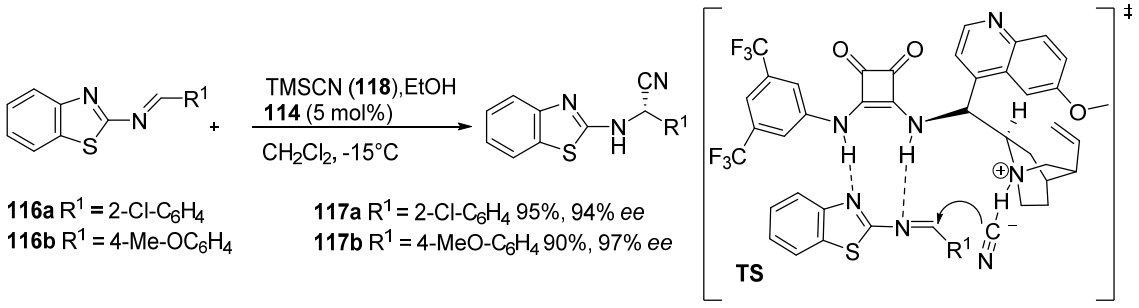
In particular, readily accessible quinine and (dihydro)quinine derived catalysts **114** and **115**, (Scheme 1.29) have received a considerable amount of attention. A select few enantioselective transformations employing these catalysts are outlined below.



Scheme 1.29 Squaramide substituted derived-cinchona alkaloid catalysts.

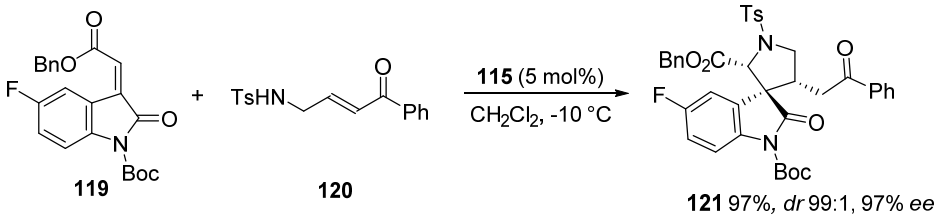
More recently, Du *et al.* have developed an efficient enantioselective Strecker reaction between imines bearing a benzothiazole moiety (*e.g*, **116a**,**b**) and TMSCN **118**, mediated by cinchona-based squaramide catalyst **114**.[101] Electron-poor and electron-rich benzothiazole imines were tested and in most the cases the desired products (**117a**,**b**)

were obtained with yields ranging from 80-99% and *ee* of up to 98%. As shown in the transition state assembly in Scheme 1.30, the squaramide moiety of **114** behaves as a Brønsted acid *via* dual hydrogen bond donation - activating the exocyclic imine (**116a**, **116b**). Meanwhile, the basic quinuclidine moiety deprotonates HCN (generated *in situ* from TMSCN and EtOH) and the resulting cyanide anion attacks the imine carbon from the most favored *re*-face, affording amino nitrile products **117a** and **117b** with excellent enantioselectivity.[101]



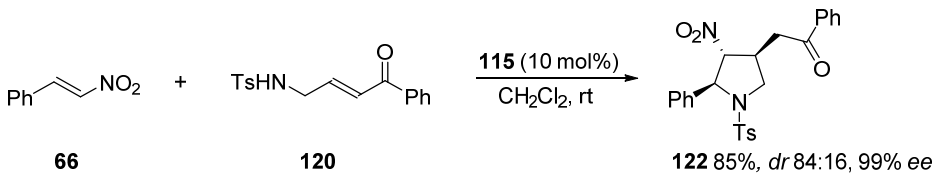
Scheme 1.30 Squaramide cinchona catalyst **114** mediates Strecker reaction.

In 2015, the same authors, employed squaramide substituted catalyst **115** for the first time in a cascade aza-Michael/Michael addition of tosylaminomethyl enone **120** to 3-ylideneoxindole **119** for the enantioselective synthesis of **121** (Scheme 1.31).[102] Although the asymmetric preparation of this scaffold would normally pose a great challenge, due to the presence of multiple stereocentres, this strategy allows for facile entry into highly functionalised spiro-compounds - a common scaffold in a range of bioactive products.[103]



Scheme 1.31 Aza-Michael reactions mediated by catalyst **115**.

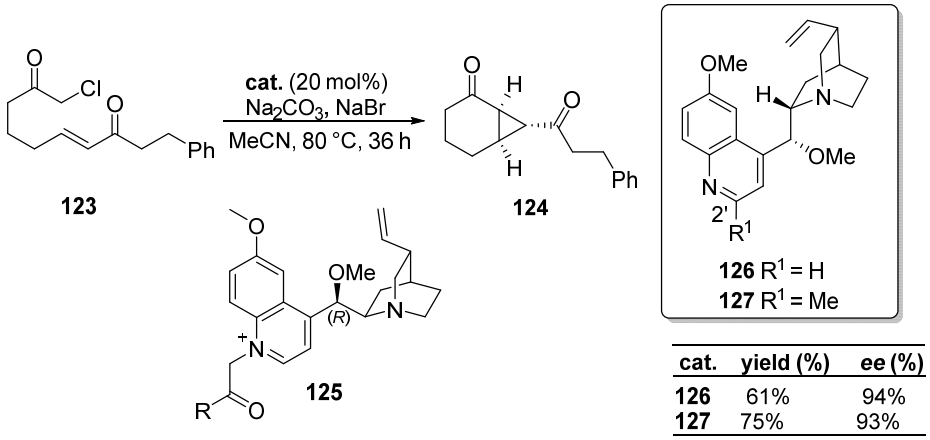
A similar stereoselective cascade aza-Michael/Michael addition was later proposed as a powerful method for the construction of chiral pyrrolidines containing three contiguous stereocentres. The catalyst **115**, once again proved to promote the cascade reaction between tosylaminomethyl enone **120** and nitrostyrene **66**, furnishing the desired product **122** in 85% yield and 99% *ee* (Scheme 1.32).[104]



Scheme 1.32 Enantioselective cascade aza-Michael/Michael reaction for the synthesis of chiral pyrrolidines.

1.3.2 Modification at C-2'

In 2006, Gaunt and co-workers published a series of studies which aimed to improve the catalysis of an intramolecular cyclopropanation reaction by developing C-2' modified cinchona alkaloids.[105] They noticed that the use of quinine and quinidine derivatives such as **126** (Scheme 1.33) in the cyclopropanation of halogenated ketone **123** furnished product **124** with high enantiomeric excesses but poor yields. They attributed the unsatisfactory yields observed to the formation of the unreactive ammonium ylide intermediate **125** (Scheme 1.33) generated by alkylation of the quinoline nitrogen with the α-haloketone. Thus, in order to prevent this side reaction, they rendered the nitrogen atom more sterically hindered by installing a methyl substituent at the C2' position. The resulting catalyst **127** was found to provide the desired product in higher yield and excellent enantioselectivity.[105]

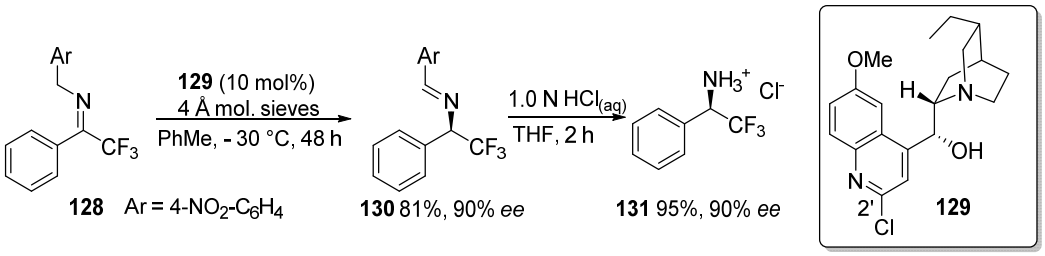


cat.	yield (%)	ee (%)
126	61%	94%
127	75%	93%

Scheme 1.33 Asymmetric intramolecular cyclopropanation promoted by cinchona alkaloid derivatives.

More recently, Deng *et al.*[106] developed a series of C-2' substituted cinchona alkaloid derivatives and investigated their catalytic activity in asymmetric isomerisation reactions

of the aromatic trifluoromethyl imine **128**. The study demonstrated that the stereocontrol of the process is influenced by the electronic properties of the substituents at C-2', as the replacement of the methyl group with a bromine or chlorine atom resulted in an increase in enantiomeric excess. Accordingly, catalyst **129** efficiently promoted the isomerisation of both aromatic and aliphatic imines to give **130** in good yield and high enantiomeric excess. Subsequent acid hydrolysis allowed access to the corresponding chiral amines **131** in high *ee* (Scheme 1.34).



Scheme 1.34 Asymmetric isomerisation of imine **128** promoted by the C-2' substituted cinchona alkaloid **129**.

Other C-2' substituted cinchona alkaloid derivatives have appeared in the literature, these have found applications in different areas of asymmetric catalysis such as aminocatalysis[107] and organometallic chemistry, where they are used as ligands.[108]

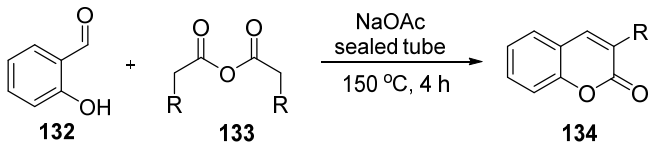
1.4 Cycloaddition reactions involving cyclic anhydrides

Historically, the use of anhydrides in synthesis has been dominated by their ability to act as electrophiles. A relatively small number of reactions involving the participation of enolisable anhydrides as nucleophiles in aldol-like coupling processes have been reported.[109] Although reactions of enolisable cyclic anhydrides as carbon-based nucleophiles in formal cycloadditions are hystorically rare, they can be extremely useful as a one-step synthesis of carbo- and heterocycles, and generate densely functionalised products (with the formation of multiple new stereocentres) including compounds of medicinal/pharmaceutical interest.[109]

1.4.1 Anhydrides behaving as carbon based nucleophiles: a historical overview

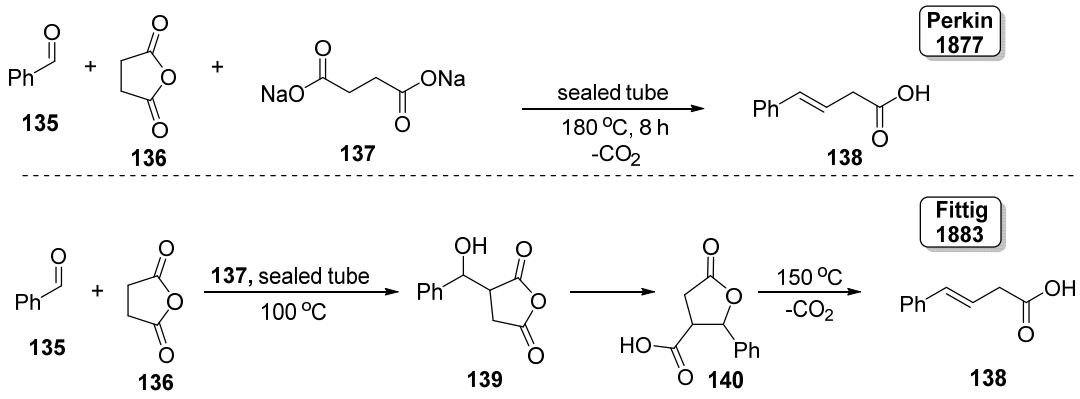
Enolisable anhydrides have long been known to react as carbon-based nucleophiles with electron deficient π-systems such as aldehydes, imines, ketones and alkenes or alkynes. The first example of an anhydride reacting as a nucleophile was reported by Perkin in

1868.[110] He found that heating enolisable anhydrides of general type **133** with salicylaldehyde **132** in the presence of a weak base afforded coumarins **134** (Scheme 1.35). [110, 111]



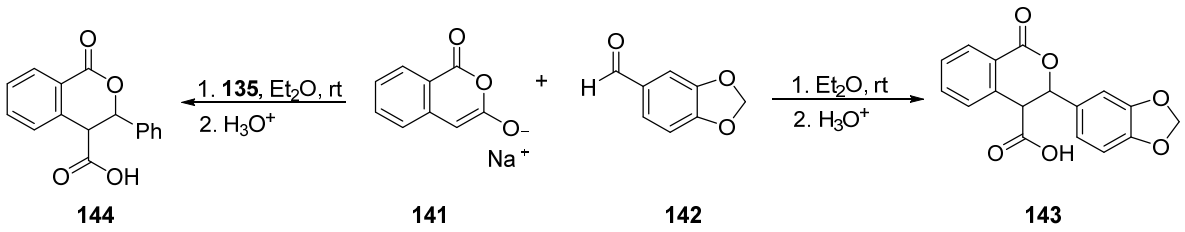
Scheme 1.35 Reaction between aliphatic anhydrides and salicylaldehyde.

One year later, he extended this work, by using cyclic enolisable anhydrides, reacting succinic anhydride (**136**) with benzaldehyde (**135**) at high temperature in the presence of sodium succinate (**137**) forming **138** after decarboxylation of the intermediate (Scheme 1.36).[112] In 1883, Fittig and co-workers repeated these reactions at lower temperatures in order to clarify the mechanism. At 100 °C they observed an initial aldol-like addition of the anhydride to the aldehyde, followed by lactonisation of the intermediate hydroxy acid **139** to give γ-butyrolactone **140**, which when heated at temperatures above 150 °C, furnished the α,β-unsaturated acid **138** upon loss of CO_2 (Scheme 1.36).[113]



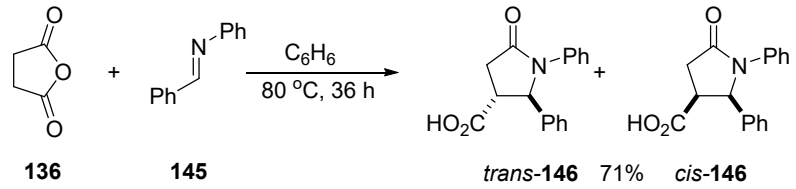
Scheme 0.36 Addition of succinic anhydride to benzaldehyde (**135**).

Besides the synthesis of γ-lactones involving succinic anhydride reported above, in 1931 Müller described the first condensation of the sodium enolate of homophthalic anhydride **141** with benzaldehyde **135** to form bicyclic dihydroisocoumarin derivative **144** (Scheme 1.37).[114] Much later, Pinder *et al*. confirmed the reactivity observed by Müller when they reacted **141** with piperonal (**142**) at room temperature to obtain the dihydroisocoumarin derivative **143** (Scheme 1.37).[115]



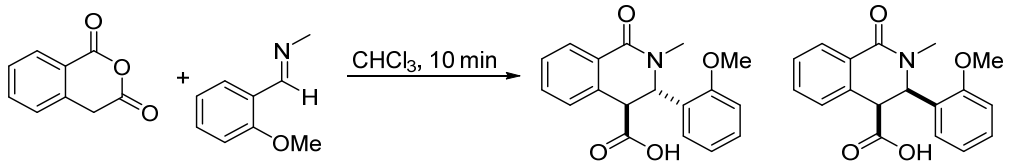
Scheme 1.37 Homophthalic anhydride enolate in a formal cycloaddition reaction with aldehydes as reported by Pinder *et al.* and Müller *et al*. respectively

In 1969, Castagnoli *et al*. reported the first examples of formal cycloaddition reactions between cyclic anhydrides and imines as a strategy for the synthesis of the the alkaloid nicotine. They observed that succinic anhydride **136** reacted under thermal conditions with aromatic *N*-benzylidenemethanamine (**145**) to form *γ*-lactam **146**, as a mixture of *trans*-**146** (major) and *cis*-**146** (minor) diastereomers in good yield (Scheme 1.38).[116] The substrate scope of this reaction was then explored employing glutaric anhydrides to form a diastereomeric mixture of *δ*-lactams in significant yield and diastereoselectivity.[117,118,119]



Scheme 1.38 Cycloaddition reaction between succinic anhydride and imine **145**.

Shortly after, Haimova *et al.*[120] and Cushman *et al*.[121] almost simultaneously reported the use of homophthalic anhydride (**147**) and derivatives in the cycloaddition reaction with imines such as **148** at room temperature as an efficient method for the synthesis of diastereomeric mixtures of dihydroisoquinolonic acids **149** (Scheme 1.39),[121] Cushman was also responsible for proposing the mechanism of the reaction in a subsequent study.[122] This process was widely explored with respect to various homophthalic anhydrides and imines, which were found to be well tolerated affording the respective products in good yields and in some cases with good diastereocontrol.



147 **148** *trans*-**149** 96% *cis*-**149**

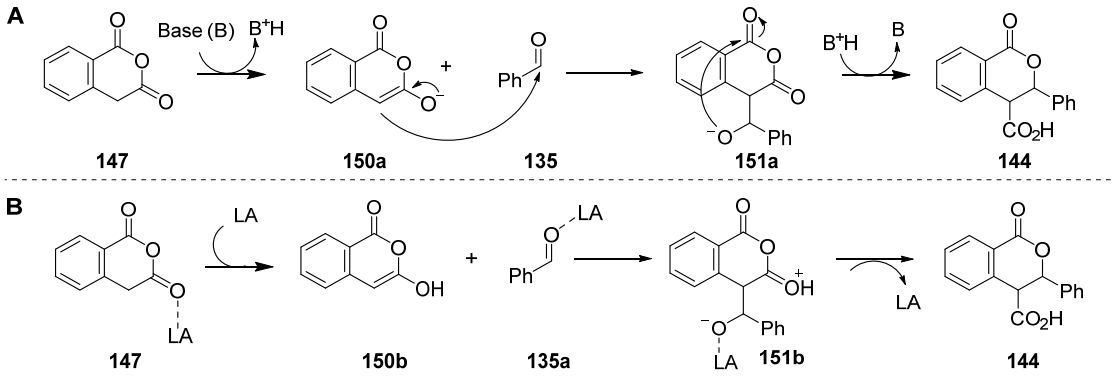
Scheme 1.39 Homophthalic anhydride in formal cycloaddition reactions with imines as reported by Cushman and Haimova.

However, some differences regarding the diastereoselectivity of the reaction were evident upon comparison of Cushman's and Haimova's reports. A few years later, Cushman explained this discrepancy by demonstrating that *cis*-isomers were kinetically favoured and could epimerise to *trans*-isomers upon heating in either xylene or acetic acid, and also during the basic extraction employed by Haimova *et al.* in their study.[120]

Cycloaddition reactions involving homophthalic anhydride were futher explored by Tamura *et al.* in 1981. They described that unsaturated (di)enones and enynes are able to react with homophthalic anhydride under thermal conditions to furnish fused aromatic products in low to moderate yield.[123,124]

1.4.2 Formal cycloaddition reactions between enolisable anhydride and aldehydes

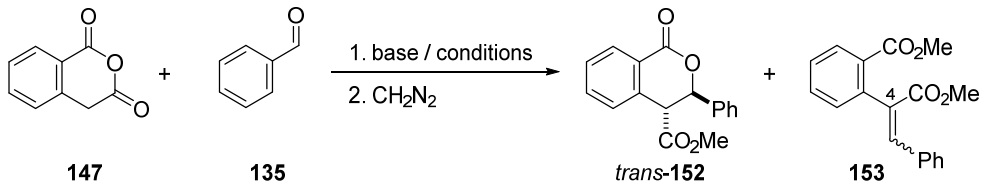
As described in preliminary reports by Fittig,[113] Müller[114] and Pinder,[115] enolisable anhydrides, in particular homophthalic anhydride, can react with aromatic aldehydes in the presence of stoichiometric amounts of either base[126,127,129] or Lewis acid.[128] Aldehydes are not nucleophilic enough to attack the anhydride, thus the reaction is believed to proceed by initial enolisation of the anhydride **147**, (promoted by a base or Lewis acid) followed by addition of the reactive enolate species **150a**,**b** to the benzaldehyde (**135**) to form a tetrahedral intermediate (**151a**,**b**), which rapidly lactonises in an intramolecular process to furnish the dihydroisocoumarin product **144** as a mixture of two diastereomers, with the *trans*-isomer generally being favoured (Scheme 1.40, **A** and **B**).[109] The rate limiting step of both processes is in the formation of the enolate species - which is favoured when aromatic anhydrides are employed (*e.g.* homphthalic anhydride), as the negative charge can be stabilised by delocalisation through the fused aromatic ring.



Scheme 1.40 Proposed mechanism of the annulation between homophthalic anhydride and benzaldehyde in the presence either base (**A**) or Lewis acid (**B**).

Inspired by Pinder's report,[116] Girotra *et al.*[125] and Nakajima *et al.*[126] independently demonstrated the application of acid/base-promoted cycloadditions in the synthesis of lactones which serve as intermediates to natural products. However, these publications lack insight with respect to both the reaction mechanism and stereochemical outcome.

In 1991, Kita and co-workers[127] first examined the possibility of promoting the cycloaddition of **147** to aldehydes *via* base-mediated reaction. They carried out a series of experiments to evaluate the effect of temperature on the reaction between homophthalic anhydride (**147**) and **135** in the presence of different bases (Scheme 1.41). The use of Na_2CO_3, as previously documented by Nakajima, formed the cycloadducts **152** and the C-4 condensed product **153** (a Perkin-type product), isolated as methyl esters after derivatisation with diazomethane.



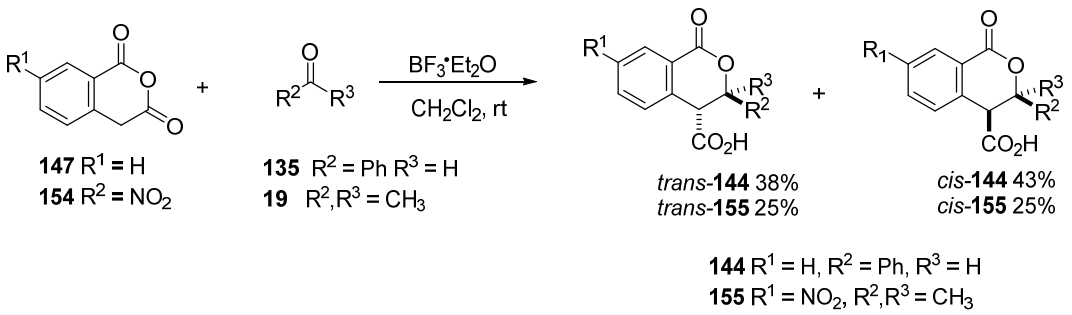
base	conditions	% yield 152	% yield 153
Na_2CO_3	benzene, rt, 24 h	35	43
NaH	THF, 0 °C to rt, 24 h	83	-
NaH	THF, 50 °C, 33 h	5	82

Scheme 1.41 Effects of base and temperature on the cycloaddition reaction.

Their focus then shifted to the use of a stronger base to promote the reaction, such as sodium hydride. As shown in Scheme 1.41, at low temperature the kinetic cycloadduct

152 was formed exclusively, while at higher temperature, under thermodynamic control, the C-4 condensed adduct **153** dominated.[127]

Gesquierre *et al*.[128] later demonstrated that stoichiometric quantities of BF_3•OEt_2 could mediate formal cycloadditions between aldehydes or ketones such as **135** and **19** and homophthalic anhydrides **147** and **154**. It was thought that the Lewis acid plays a dual role in activating the aldehyde by coordination to the oxygen atom, and inducing enolate formation by binding to the anhydride. This approach proved to be extremely efficient as it affords the desired products (*e.g.* **144** and **155**) as a mixture of *cis* and *trans* diastereomers in good yields by suppressing the formation of the C-4 condensed adduct which dominates product mixtures when the reaction is not conducted at low temperature (Scheme 1.42).

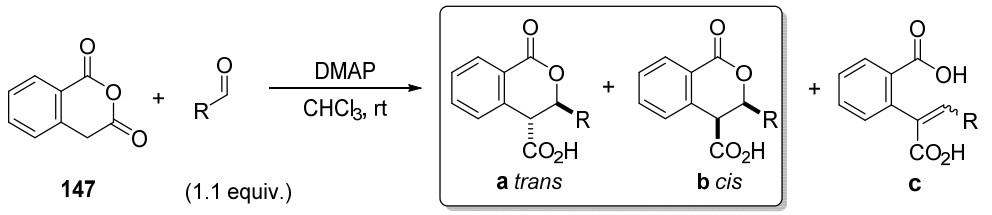


Scheme 1.42 Cycloaddition reaction between homophthalic anhydrides and aldehydes/ketones promoted by BF_3•OEt_2.

A similar transformation was subsequently reported by Palmavera and co-workers,[129] who investigated the catalytic performance of 4-dimethylaminopyridine (DMAP) under mild conditions. The authors evaluated the reaction of homophthalic anhydride with a wide variety of aromatic and heteroaromatic aldehydes in the presence of stoichiometric amounts of DMAP at room temperature (Scheme 1.43). The reaction proceeded swiftly, affording a mixture of two diastereomers with a general preference for the formation of the *trans*-isomers. Unlike the previous studies, diastereoselectivities were measured by ^{1}H NMR spectroscopic analysis of the crude mixture after work up.

As shown in Scheme 1.43, the use of either benzaldehyde (**135**) or substituted benzaldehydes bearing electron-widrawing groups (*e.g.* **156**) formed cycloadducts **144a,b** and **159a,b** respectively in yields of up to 98% with an approximate *dr* of 2:1. In cases where the aldehyde is substituted with a heterocyclic ring, such as furan-2-yl **158**,

the C-4 methylene condensed product **161c** was detected in quantities of up to 30% along with the diastereomeric mixture of **161a,b**. Formation of the side product **160c**, albeit at low quantities (<10%), was also observed when the electron-rich aldehyde **157** was employed.[129]



135 R = C_6H_5
156 R = 4-NO_2-C_6H_4
157 R = 4-MeO-C_6H_4
158 R = 2-furanyl

144 R = C_6H_5
159 R = 4-NO_2-C_6H_4
160 R = 4-MeO-C_6H_4
161 R = 2-furanyl

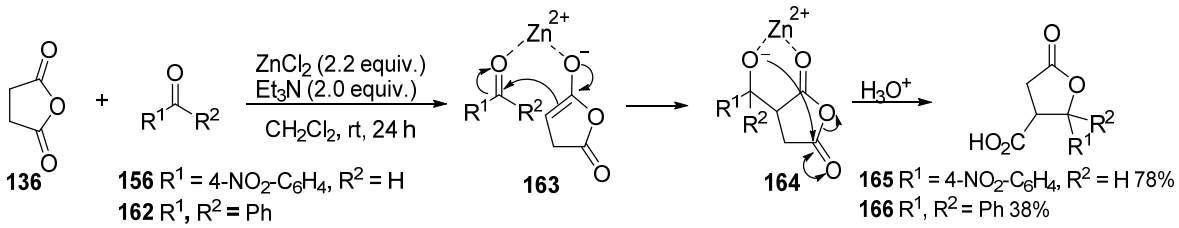
prod.	time (h)	% yield	% ratio (a:b:c)
144	2	100	70:30:0
159	2	98	77:30:0
160	2.5	98	80:16:4
161	1.5	100	62:8:30

Scheme 1.43 Cycloaddition between homophthalic anhydride (**147**) and aldehydes catalysed by DMAP.

1.4.2.1 Expansion of the scope of the reaction: the anhydride component

Aldehydes have been employed in formal cycloaddition reactions in conjunction with several cyclic anhydrides, however the substrate scope of these reactions is considerably limited, largely being restricted to aromatic aldehydes and succinic or homophthalic anhydrides. As mentioned in Section 1.4.2, structurally simpler anhydrides devoid of a stabilising group (*e.g.* succinic anhydride) generally require strong acids/bases or harsh reaction conditions to allow for the synthesis of lactones in moderate yields and diastereoselectivities.

In 1983, Lawlor *et al.*[130] carried out a series of studies aiming to optimise the reaction between succinic anhydride and aromatic aldehydes, just carried out by Fitting *et al.* some years earlier.[113] They developed a strategy in which a series of aromatic aldehydes/ketones such as **156** and **162** reacted with **136** in the presence of a Lewis acid (*e.g.* $ZnCl_2$) and triethylamine (Scheme 1.44). This methodology furnished derivatives of paraconic acid[131] **165** and **166** respectively, *via* intermediates **163** and **164**, in greater yields compared to those achieved in the Perkin-Fittig condensation itself.[112,113]

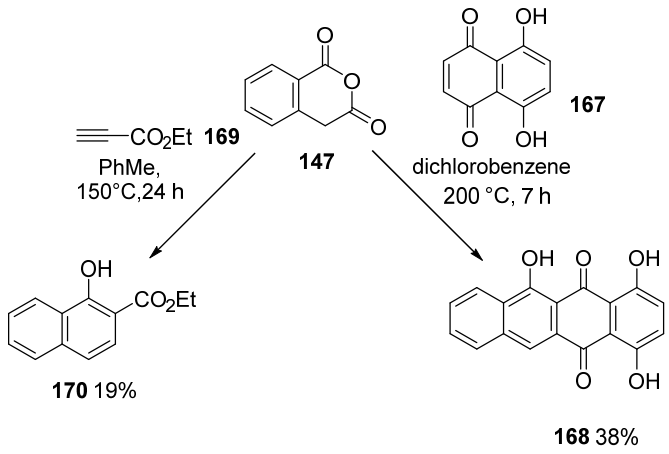


Scheme 0.44 Lewis acid/base-catalysed cycloaddition reaction of succinic anhydride (**136**) to aldehydes and ketones.

The use of weak bases (*e.g.* sodium acetate) under thermal conditions was also investigated, however low yields and poor stereoselectivities were reported.[132,133,134] Formation of the enolate of substituted succinic anhydrides in the cycloaddition reaction with aldehydes can also be promoted by strong hindered bases such as lithium alkoxides[135] or LiHMDS (and Na^+/K^+ salts thereof),[136,137,138]which furnishes products in greater yield and diasterocontrol.

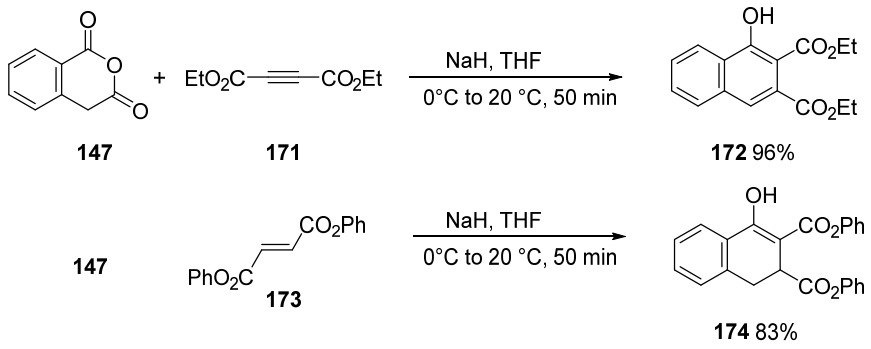
1.4.3 Formal cycloaddition reactions with other electrophiles

In 1981, Tamura *et al.*[123,124] demonstrated for the first time that homophthalic anhydride **147** reacts readily with activated alkynes (*e.g.* **169**), and unsaturated carbon-carbon multiple bond moieties (**167**) at high temperature, leading to the formation of fused aromatic products such as **168** and **170** in a regioselective manner, although in low to moderate yields (Scheme 1.45).



Scheme 1.45 Cycloaddition of homophthalic anhydride to carbon-carbon multiple bonds.

Later on, a base promoted version of this reaction was developed by the same authors, who demonstrated that the use of strong bases such a lithium diisopropylamide (LDA) or sodium hydride (NaH) allowed the reaction to proceed smoothly under milder conditions to furnish products (*e.g.* **172**, **174**) in greater yields compared to those obtained under thermal conditions (Scheme 1.46).[139] This strategy was extended to a variety of alkenes (*e.g.* **173**) and alkynes such as **171**, generally requiring electron-withdrawing groups at both termini to render highly functionalised products in good yields.[139]

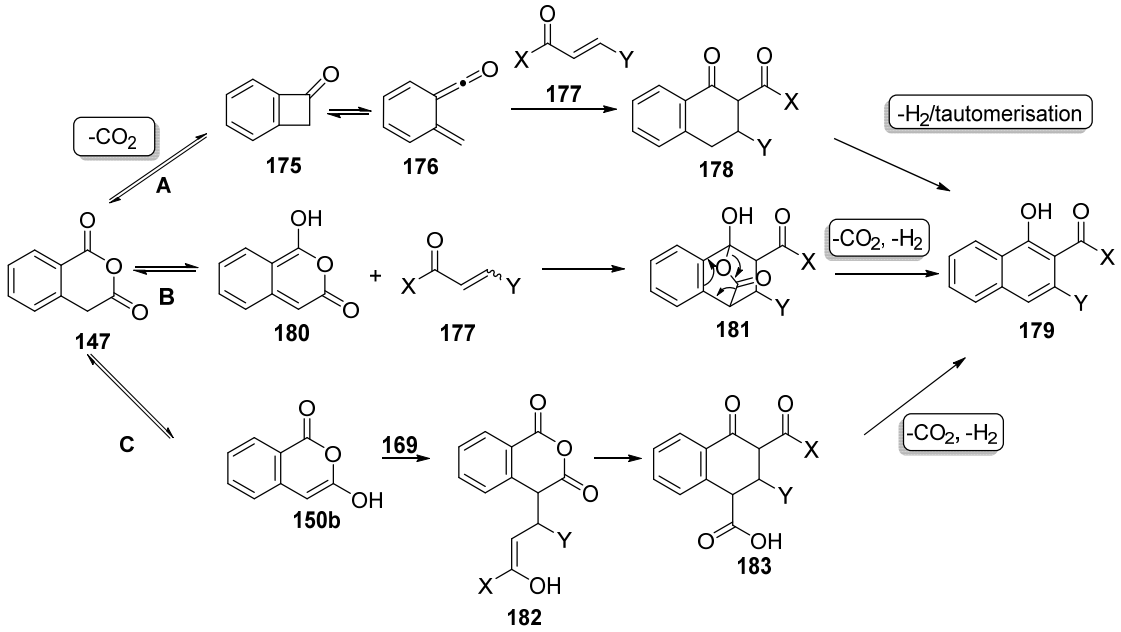


Scheme 1.46 Cycloaddition reaction between homophthalic anhydride and different electrophiles promoted by strong bases.

In order to explain the mechanism of the reaction and its observed regioselectivity, Tamura *et al*. initially proposed two possible pathways,[123] followed by a third mechanism two years later.[124]

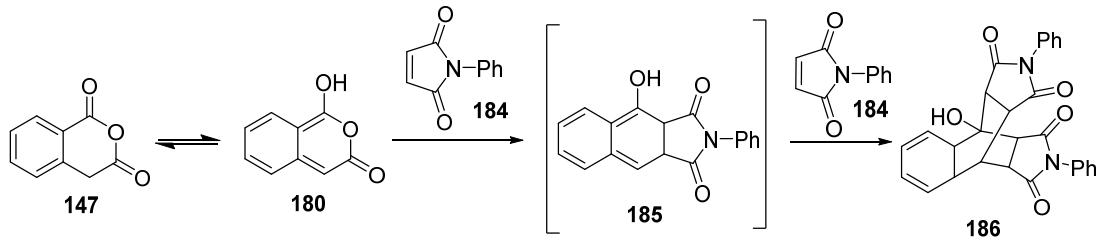
The first proposed mechanism speculated that the intermediate **175**, generated *via* decarboxylation of **147**, undergoes an electrocyclic ring opening and subsequent concerted thermal [4+2] cycloaddition with the dienophile **177**, to form the cycloadduct **178**, which undergoes elimination of molecular hydrogen and tautomerisation to the aromatic product **179** (**A**, Scheme 1.47).[123]

However, this mechanism was deemed improbable when prolonged heating of the reaction mixture containing **147** in dichlorobenzene failed to form **175** or **176**, and homophthalic anhydride was recovered from the process unchanged.[123]



Scheme 1.47 (**A**) Proposed [4+2] cycloaddition mechanism (**B**) Diels-Alder cycloaddition. (**C**) Step-wise Michael addition/ring closure mechanism.

The second pathway postulated that C-C bond formation may proceed *via* an initial Diels Alder cycloaddition between the conjugated dienol tautomer of **147** (*e.g.* **180**) and the electrophile **177** to afford **181**, which after decarboxylation and tautomerisation affords **179** (**B**, Scheme 1.47).[123] The formation of **180** was supported by the isolation of adduct **186**, formed by the cycloaddition of *N*-phenylmaleinimide **184** with the conjugate enol intermediate **185**, which was derived from to the dienol tautomer intermediate **180** (Scheme 1.48).[124]

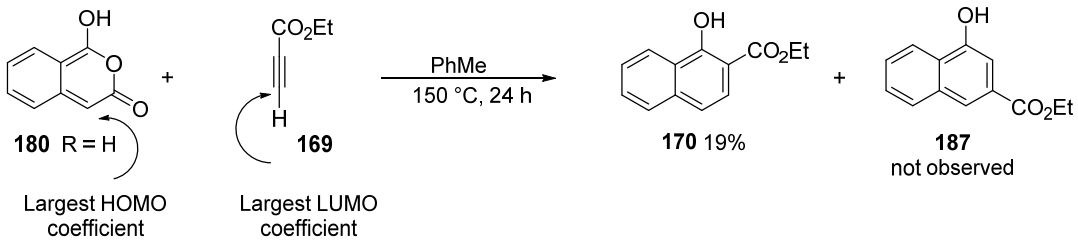


Scheme 1.48 Evidence favouring the Diels-Alder cycloaddition pathway.

The third postulated mechanism involves the Michael addition of the enol of **147** (*e.g.* **150b**) to dienophile **177** to furnish Michael adduct **182**, which undergoes intramolecular cyclisation to the cycloadduct **183**. Subsequent decarboxylation and elimination of molecular hydrogen followed by tautomerisation affords the product **179** (**C**, Scheme

1.47).[124] However, a brief mechanistic study by Tamura *et al.* later rejected this pathway when the lithium enolate of homophthalic anhydride failed to react with several well known Michael acceptors.[139b] Thus, all evidence reported by Tamura *et al.* to date strongly supports the Diels-Alder mechanism, however the stepwise route C cannot be totally excluded.[139b]

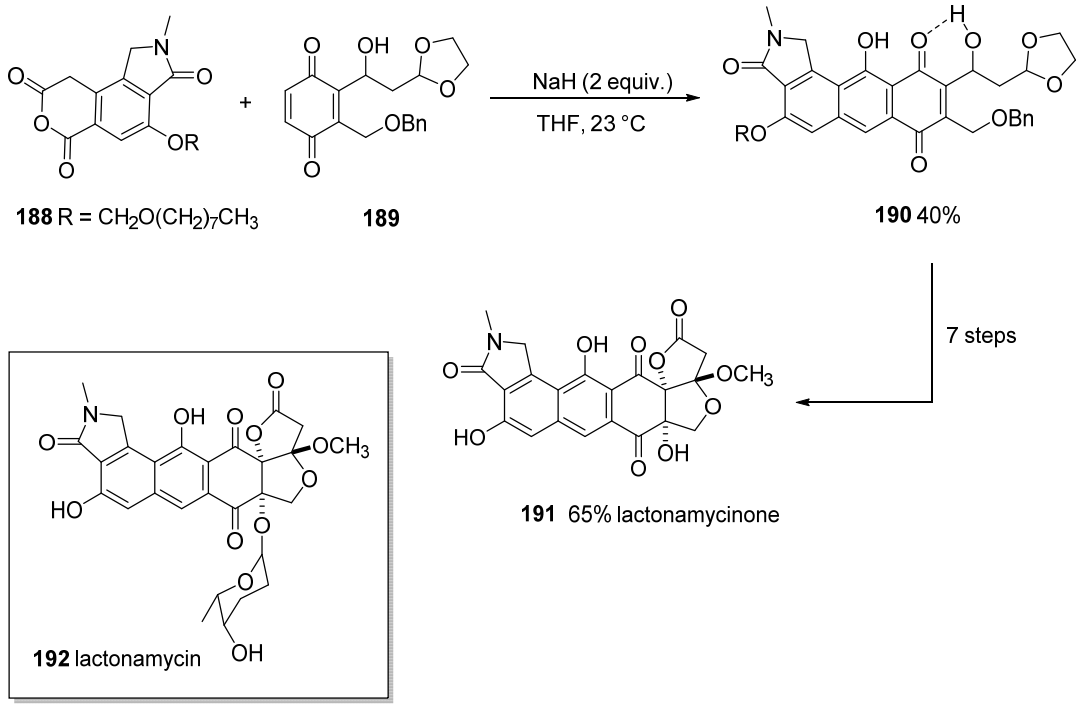
In regiochemical agreement with the Diels-Alder model, **170** was formed exclusively in the cycloaddition between **180** and **169**, with no formation of regioisomer **187** under the reported conditions (Scheme 1.49).[123] The most efficient orbital overlap occurs between the nucleophilic carbon of the diene **180** (bearing the largest HOMO coefficient) and the unsubstituted alkyne carbon of **169** (possessing the largest LUMO coefficient).[140,141]



Scheme 1.49 Regioselective cycloaddition reaction between **180** and dienophile **169**.

Over the years the versatility of this protocol has been exploited by Tamura and several other groups in the total synthesis of natural products, namely antracyclinones- precursors of antibiotics which have also proven medicinally valuable in the treatment of a range of human cancers.[142,143,144]

This process has also been utilised in the construction of highly functionalised aromatic systems, and was successfully employed by Danishefsky and co-workers in the synthesis of **191** as an aglycone intermediate of the antibiotic lactonamycin (**192**).[145] The reaction of homopthalic anhydride derivative **188** with 2 equiv. of quinone **189** in the presence of sodium hydride afforded the tetracyclic intermediate **190** in moderate yield and high regiocontrol due to hydrogen-bond activation from the unprotected hydroxyl group on the side chain of **189** (Scheme 1.50).[146]



Scheme 1.50 Lactonamycinone synthesis developed by Danishefsky and co-workers.

Although strong bases were widely employed in most total syntheses involving this process, in 1991, Smith *et. al.*[147] demonstrated that a 15% loading of triethylamine could promote the reaction between 3-methoxyhomophthalic anhydride and substituted alkynes to provide naphthalene derivatives in good yields.

1.5 Catalytic asymmetric reactions involving enolisable anhydrides

Over the past several decades, formal cycloaddition reactions of enolisable anhydrides to various electrophiles have been investigated extensively, having been employed in key transformations in the total syntheses of natural products[109] and drug leads.[148] Despite the fact that these annulation reactions generally form two stereocentres, and in spite of the high synthetic potential of the densely functionalised heterocyclic core formed (which is present in a broad range of natural products and other molecules of medicinal/pharmaceutical interest),[149,150] until very recently[151,167] no asymmetric variant of formal cycloaddition reactions with aldehydes or other electrophiles had been reported The recent studies which aimed to develop asymmetric variants of these reactions will be discussed in the next Section.

1.5.1 Organocatalytic cycloaddition reaction between homophthalic anhydride and aldehydes for the synthesis of chiral dihydroisocoumarin cores

3,4-Dihydroisocoumarins are a structurally diverse class of natural lactones exhibiting a broad spectrum of biological activity. A considerable amount of work has been published detailing their chemistry and biology, and a number of natural and synthetic molecules containing the 3,4-dihydroisocoumarin cores have been shown to exhibit significant pharmacological activities ranging from antimicrobial to anticancer[152,153,154] and anti-HIV.[155] The majority of these natural products share common structural feautures such as a hydroxyl group at the C-8 position, and a chiral center at the C-3' which generally bears alkyl, alkenyl or aryl groups. The structures of some of the members belonging to this class of compounds are depicted in Figure 1.8.

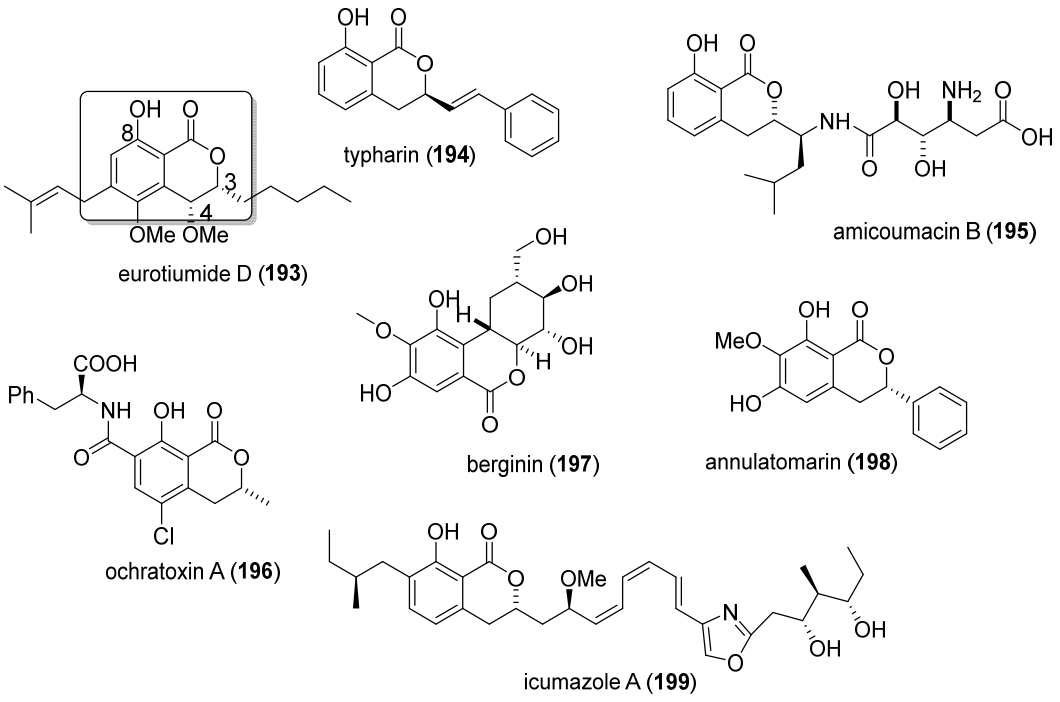
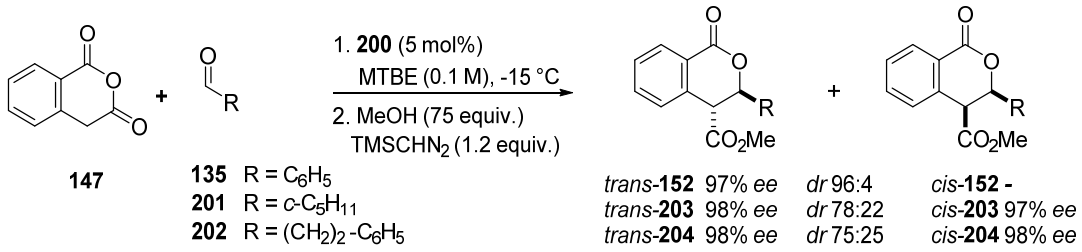
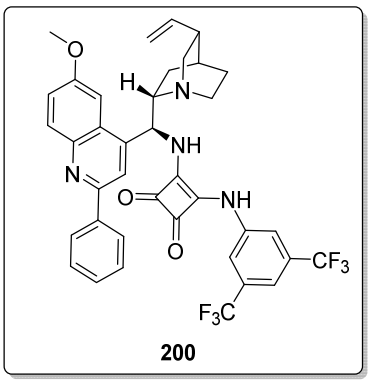


Figure 1.8 Selected natural products containing the 3,4-dihydroisocoumarin framework.

As with other classes of natural products, several novel asymmetric methodologies[156,157,158] have been developed during the course of synthesis of these compounds. However, most procedures suffer numerous drawbacks such as having too many steps, low yields due to formation of side products, and/or a requirement for harsh reaction conditions.

In 2012, Connon and co-workers reported the first asymmetric cycloaddition reaction of enolisable anhydrides to aldehydes in the presence of a chiral bifunctional organocatalyst, yielding a one-step synthesis of the dihydroisocoumarin structure with the formation of two adjacent stereocenters. The screening of a range of (thio)urea and squaramide cinchona alkaloid-derived catalysts demonstrated that the reaction between homophthalic anhydride (**147**) and benzaldehyde (**135**) catalysed by a novel squaramide **200** generated the lactone **152** with a preference for the *trans*-stereoisomer in 98% yield, good diastereoselectivity and 97% *ee* under mild conditions (Scheme 1.51).[151]





Scheme 1.51 Asymmetric cycloaddition reaction between homophthalic anhydride and benzaldehyde under optimal conditions.

Using these above conditions, the scope of the reaction with respect to the aldehyde component was investigated. Electron-deficient and electron-rich aromatic aldehydes, as well as hindered and heterocyclic aldehydes were all well tolerated. In addition, the effect of substitution on the homophthalic anhydride's aromatic ring was also investigated (-NO_2, -Br and –OMe). As expected, electron-withdrawing, as opposed to electron–donating groups on the ring brought about faster reactions, as electron-withdrawing groups would stabilise the enol – leading to greater concentrations in solution. This observation supports the idea that the anhydride – enol tautomeric equilibrium has a key

influence on the reaction rate in the catalytic process. It is noteworthy that while the diastereoselectivity is uniformly excellent in the case of aromatic aldehydes, the use of both more hindered and straight-chain aldehydes such as **201** and **202** leads to decreased levels of the *trans*-diastereomers (*e.g.* **203**, **204**) over the *cis*-diastereomers (*e.g.* **203**, **204**), which were both obtained in remarkable enantiomeric excess.[151]

1.5.1.1 Stereochemical outcome: proposed mechanism

In order to explain the mechanism and the stereochemical outcome observed in the previous studies, the authors initially proposed two plausible pathways for the reaction between homophthalic anhydride and benzaldehyde in the presence of catalyst **200**.[151] One possibility is a specific catalysis-like mechanism in which the quinuclidine moiety deprotonates the homophthalic anhydride to form the enolate (Figure 1.9). This species, once stabilised through double H-bonding by the squaramide unit, reacts with the aldehyde which has been activated by the protonated quinuclidine in the key stereocentre forming step. In the second possible catalyst binding mode, the catalyst promotes the reaction *via* general acid/base catalysis, in which the enol tautomer of the anhydride is held in place by a hydrogen bonding interaction with the quinuclidine nitrogen atom, while the aldehyde is activated by hydrogen bond donation from the squaramide moiety (Figure 1.9). Computational studies later carried out by Connon *et al.*[159] were able to discriminate between these mechanisms on the basis of there being a higher energetic barrier associated with enol formation and C–C bond formation in a concerted general-catalysis scenario, which allowed the authors to rule out this route.

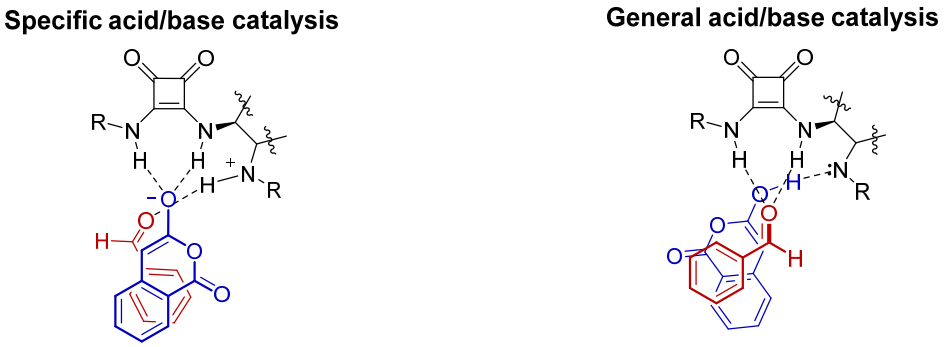


Figure 1.9 Proposed generic mechanisms: specific acid/base catalysis and general acid/base catalysis.

In agreement with experimental results, computational studies revealed the pathway leading to formation of the major *trans*-(*R*,*R*) diastereomer to be favoured. The stereochemical outcome was found to be controlled by the attractive interactions between the catalyst's quinuclidine/C'-2 quinoline rings and the anhydride oxygen atoms, which facilitate the binding of the enolate to the squaramide moiety in a selective fashion. Thus, only a single enolate face is available to attack the aldehyde, which directs its phenyl moiety into empty space away from the squaramide moiety in order to minimise steric clashes with either the catalyst quinuclidine/quinoline rings or the anhydride itself (Figure 1.10). It is important to note that the C-2' phenyl ring stabilises the hydrogen-bonding interactions between the squaramide moiety and the anhydride through an attractive C-H interaction between the aryl unit and anhydride oxygen atom - pointing out a key role that this modification may play in cinchona-based catalysis.

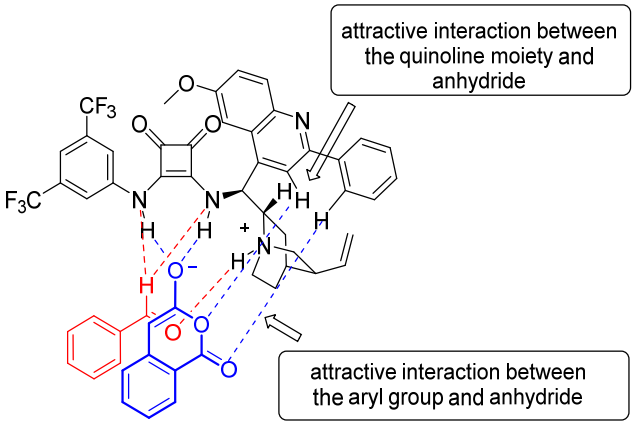


Figure 1.10 Proposal stereochemical outcome.

1.5.2 Organocatalytic cycloaddition reaction between phenyl succinic anhydride derivatives and aldehydes

Another common building block present in many natural products is that of γ-butyrolactones [160,161] - being particularly abundant in fungi, lichens and bacteria. A wide variety of these compounds are naturally occurring as mono-, di- and trisubstituted monocyclic paraconic acids, but are also found as part of more complex frameworks especially within bi- and tricyclic ring systems as shown in Figure 1.11. A broad biological profile including antibiotic, antihelmitic, antifungal, antitumor, antiviral, antiinflammatory and cytostatic properties[162] make γ-butyrolactones interesting lead structures for the discovery of new pharmaceutical compounds.

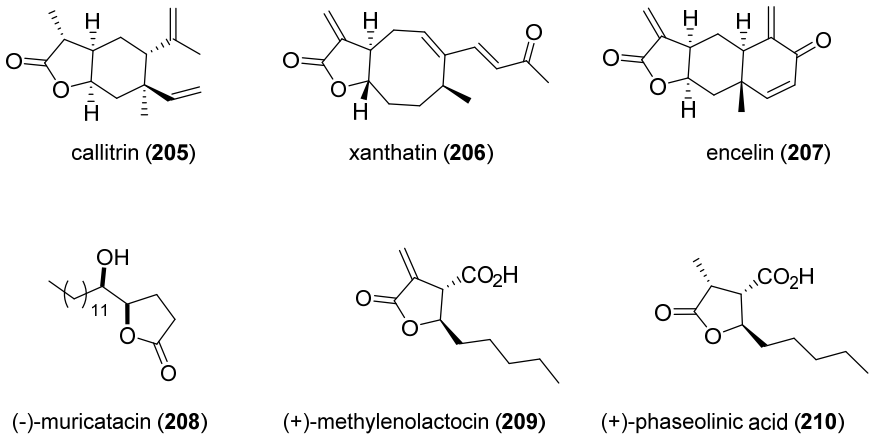
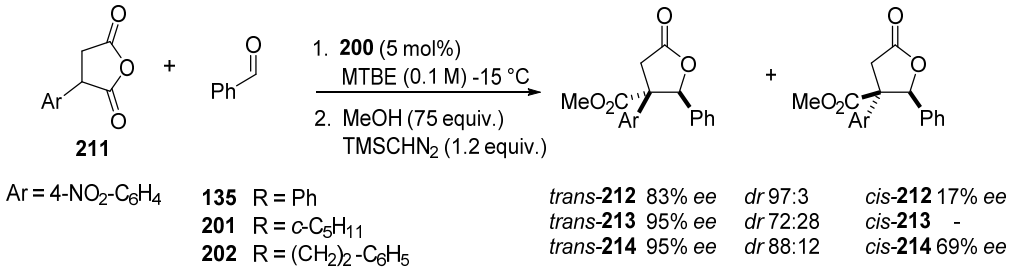


Figure 1.11 Selected natural products containing the *γ*-butyrolactone unit.

Consequently, a number of stereoselective syntheses have been developed which allow for the construction of a variety of paraconic acids in their racemic and enantiopure forms. Most of the asymmetric approaches involve the use of chiral pool (especially carbohydrates and sesquiterpene lactones),[163,164] chiral auxiliaries (*e.g.* acyloxazolidinone),[165] and catalytic asymmetric strategies such as Sharpless epoxidations.[166] Although all the aforementioned strategies afford the desired enantioenriched *γ*-butyrolactones in good yield, they generally suffer limitations such as reduced functional diversity of products and involvement of complex multi-step procedures.

Retrosynthetic disconnection of a lactone shows that their synthesis may be achieved *via* a formal cycloaddition between enolisable cyclic anhydrides and aldehydes. Due to a lack of any effective asymmetric methodology for this transformation, recently Connon *et al.* went about an intense investigation into the development an efficient and versatile asymmetric organocatalytic protocol able to furnish densely functionalised lactones with the simultaneous formation of up to two new stereocentres in a single step.[167]

In 2012, it was demonstrated that under mild conditions, catalyst **200** can provide one-pot access to functionalised *γ*-butyrolactones in high yield and good-excellent stereocontrol by promoting the cycloaddition between phenyl succinic derivatived anhydrides and aldehydes (Scheme 1.52).[167]



Scheme 1.52 Aymmetric cycloaddition reaction between *p*-nitrophenyl succinic anhydride and benzaldehyde under optimal conditions.

Consistent with the observations made in the cycloaddition reaction with homophthalic anhydride derivatives, it was reported that introduction of electron-withdrawing and donating groups on the aromatic ring of phenylsuccinic anhydride resulted in a significant variation in reactivity, and allowed the identification of 4-nitrophenyl succinic anhydride (**200**) as an optimum substrate for the subsequent investigation of the reaction scope with respect to the aldehyde component. Reactions involving simple aromatic and heteroaromatic aldehydes furnished the desired products (*e.g.* **212**) with moderate to excellent diastereo- and enantioselectivity, whereas hindered and aliphatic aldehydes such as **201**, **202** led to increased amounts of the *cis*-diastereomer being isolated (*e.g.* **213**, **214**).

1.5.3 Kavalactones as important building blocks in natural products

Kavalactones are a class of natural products isolated from the roots and rhizomes of the kava plant Piper methysticum - widespread in the South Pacific islands.[168] The extract of this plant contains several active compounds known as kavapyrones,[169] which exhibit significant biological activity including sedative, anticonvulsive, anaesthetic, and anxiolytic properties.[170] These compounds present a common 3,4-dihydropyrone core (Figure 1.12), usually bearing a methoxy-group at C-5', and a lipophilic chain or heteroaromatic ring at C-3'. Hydroxyl functionalities substituted with a glycoside unit at C-4' have also been observed. Although a number of the kavalactones are achiral, the majority of them possess a single stereogenic centre at C-3'.

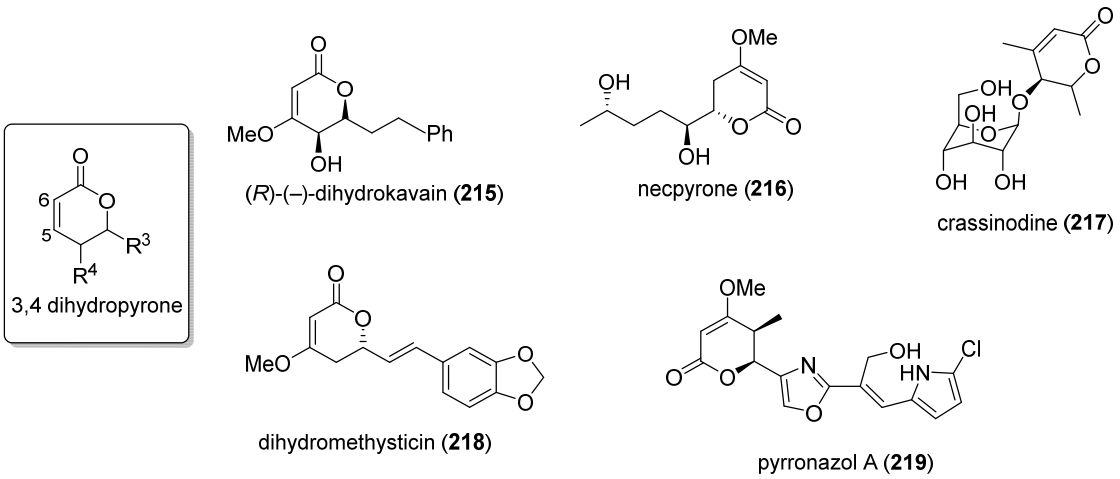


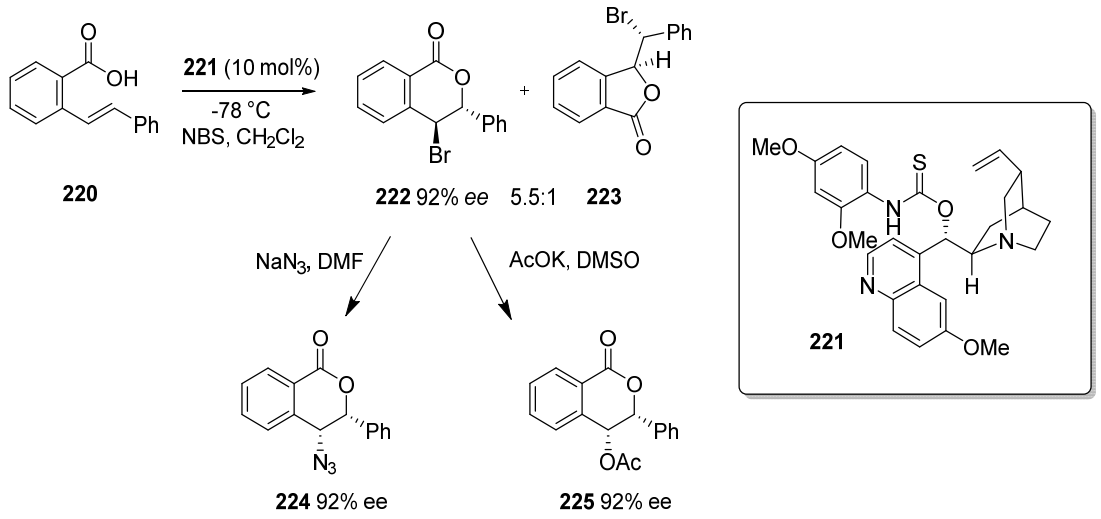
Figure 1.12 Selected natural products containing the 3,4 dihydropyrone unit.

The valuable pharmacological activity of kavalactones mentioned previously has sparked the development of several synthetic procedures for their synthesis, such as aldol reactions of *N*-acetyl thiazolidinethiones followed by a malonate displacement/decarboxylation,[171] asymmetric hydrogenation of *β*-ketoesters mediated by a Ru-(+)-BITIANP catalyst,[172] and enantioselective hydrogenation of 4-alkoxy and 4-methyl derivatives of 2-pyrones to the corresponding dihydro analogues by cinchona-modified Pd/TiO_2,[173] to name a few.

A retrosynthetic disconnection of the kavalactone functionality shows that synthesis of the 3,4 dihydropyrone unit, may again be achieved by formal cycloadditions between cyclic anhydrides and aldehydes (see Chapter 4, Section 4.7).

1.5.4 Accessing *cis*-dihydroisocoumarins

As previously mentioned in Sections 1.5.1 and 1.5.2, it has been observed that the diastereoselect ivity of the anhydride-aldehyde cycloaddition process is effected in favour of the *cis*-product when sterically hindered or linear aliphatic aldehydes were employed. Despite *cis*-dihydroisocoumarin being a fundamental unit found in many compounds possessing a wide range of biological activity[149-155] (see Section 1.5.1), only one asymmetric synthesis of the *cis*-diastereomer had been reported in the literature.



Scheme 1.53 Bromocyclisation of styrene-type carboxylic acids promoted by catalyst **221**.

In 2011, Yeung and co-workers[174] reported an enantioselective approach to the synthesis of *cis*-3,4-dihydroisocoumarins *via* a bromocyclisation of styrenyl carboxylic acid **220** promoted by amino-thiocarbamate cinchona alkaloid-derived catalyst **221**. This procedure allowed for the formation of **222** in 92% *ee* in which the bromine atom can be readily converted to other functional groups, affording *cis* configured products such as **224** and **225** -core structures present in an inhibitor of cyclooxygenase-2 and an aldosterone synthase inhibitor respectively (Scheme 1.53). Although this methodology rendered a synthesis of biologically active molecules, several limitations, such as the need for low temperature, poor regioselectivity (as the 5-*exo* product **223** was also observed), intolerance to aliphatic substituents, and a need for late stage nucleophilic substitution of bromine to obtain the *cis*-diastereomer were evident. Very recently the same authors were able to control the regioselectivity of the process by using catalytic amounts of trifluoroacetic acid, giving an 6-*endo*:5-*exo* ratio of up to 99:1.[175] However, no regioselective asymmetric synthesis of these products was developed *via* this method.

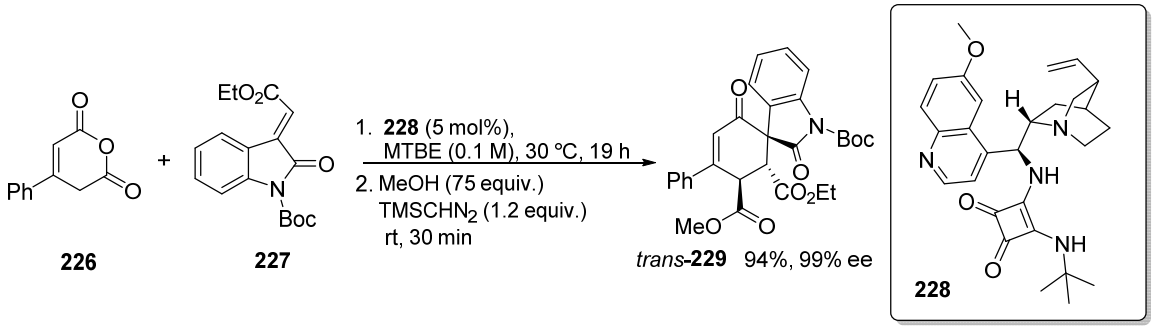
1.5.5 Asymmetric cycloaddition reactions between Michael acceptors and enolisable anhydrides

As documented in Section 1.4.3, the reaction between homophthalic anhydride and carbon based electrophiles has been widely studied by Tamura *et al.,*[124-125] however neither efficient catalytic nor asymmetric variants of this process were developed until 2013.

In that year, Ye and co-workers[176] reported a cinchona alkaloid-catalysed enantioselective [4+2] cycloaddition between *α,β*-unsaturated acyl chlorides and electron-deficient alkenes derived from oxindole to give the corresponding spirocarbocyclic oxindoles in good yields with high diastereo- and enantioselectivities.

Around this time, based on the results obtained from their seminal studies on the asymmetric cycloaddition between homophthalic anhydrides and aldehydes, Connon *et al*.[177] hypothesised a similar process, in which a Michael acceptor takes the role of the electrophile, may be developed.

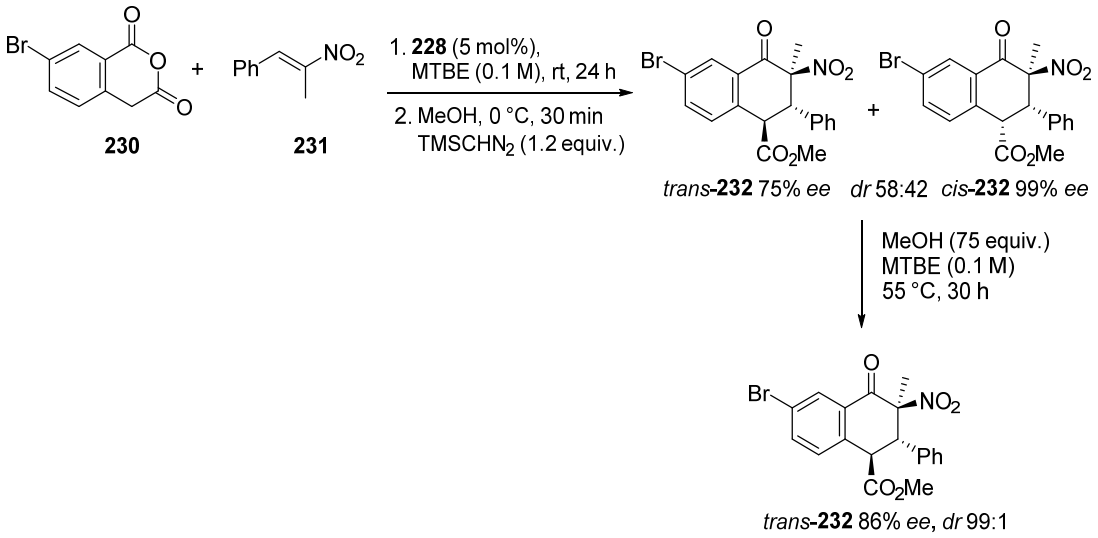
This later came into fruition when they reported the asymmetric Tamura cycloaddition between phenyl glutaconic anhydride **226** and substituted alkylidene-2-oxindole **227** in the presence of *tert*-butyl-substituted squaramide-based catalyst **228** to give one-step access to densely functionalised 3,3-spirooxindole **229** (Scheme 1.54), which are recognised as a privileged core given their wide and promising biological activity in various therapeutic areas.[103]



Scheme 1.54 Asymmetric Tamura cycloaddition between phenyl glutaconic anhydride **226** and substituted alkylidene-2-oxindoles **227**.

More recently, Connon and co-workers were able to extend the scope of the electrophile in this process to a range of trisubstituted nitroalkenes. In the presence of the bulky squaramide-based bifunctional catalyst **228**, anhydride **230** reacted with **231** to afford bicyclic structures **232** bearing three contiguous stereogenic centres, including one all-carbon quaternary in good yield and enantiocontrol, however in poor *dr* (Scheme 1.55).[178] A subsequent computational study of this reaction was able to elucidate an epimerisation process which was observed in methanol in the absence of catalyst **228** (*via* proton

transfer at the *α*-carbon to the ester functionality) which converts the *cis*-diastereomer to the *trans* with concomitant improvement in enantioselectivity.[178]



Scheme 1.55 Enantioselective cycloaddition reaction between anhydride **230** and trisubstituted nitroalkene **231**.

1.6 Kinetic and dynamic resolution: a general introduction

Kinetic resolution is defined as a process in which the enantiomers of a racemic substrate (*S*) react with a chiral reagent (*e.g.* catalyst, solvent) at different rates, forming two diastereomeric transition states.[179] The difference in energy between the transition states (ΔE_a) associated with the slow and the fast reacting enantiomers (*R* and *S* respectively, Figure 1.13) determines the preferential reaction of one enantiomer over the other to give a separable mixture of enantioenriched starting material and product.

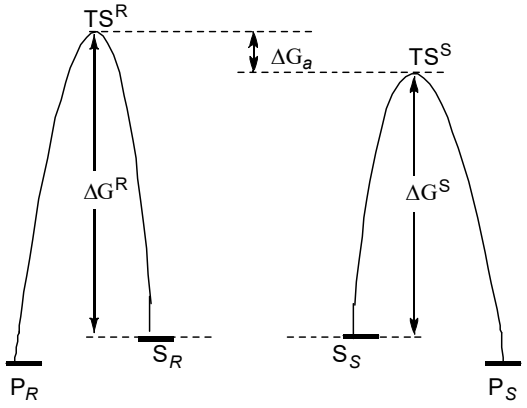


Figure 1.13 Theoretical free energy diagram for kinetic resolution.

The efficiency of a kinetic resolution is expressed in terms of selectivity factor (S), which is a ratio of the rate constants for the reaction of each substrate enantiomer with the chiral agent ($k_{rel} = k_{fast}/k_{slow}$), and is directly related to $\Delta\Delta G^{TS}$ according to eq. 1.1.[180]

$$S = k_{rel} = k_{fast}/k_{slow} = e^{\Delta\Delta G/RT} \qquad \text{(eq. 1.1)}$$

Conveniently, S can be calculated by eqs. 1.2 or 1.3, where C stands for conversion ($0 \leq C \leq 1$) while *ee* and *ee*' ($0 \leq ee$ and $ee' \leq 1$) are the enantiomeric excesses of recovered starting material and product respectively.[180]

$$S = \frac{\ln[(1-C)(1-ee)]}{\ln[(1-C)(1+ee)]} \qquad \text{(eq. 1.2)}$$

$$S = \frac{\ln[1-C(1+ee')]}{\ln[1-C(1-ee')]} \qquad \text{(eq. 1.3)}$$

Under normal conditions, enantioselective reactions of prochiral substrates yield products with constant *ee*, however in a kinetic resolution process the *ee* of both starting material and product changes as a function of conversion (Figure 1.14).[181]

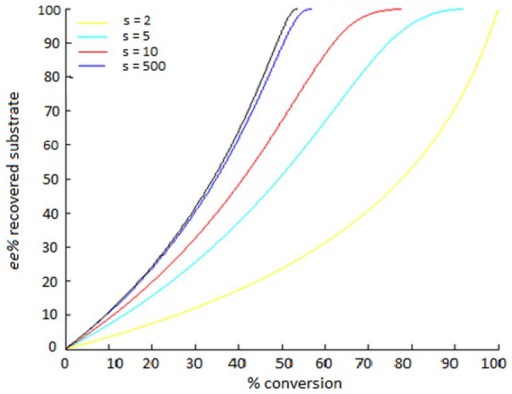


Figure 1.14 Plot of substrate *ee* vs. conversion for different S values.[181]

As the reaction proceeds, the *ee* of the starting material increases with the opposite observed for the product. The k_{rel} value determines the extent of substrate conversion necessary to obtain a target *ee*, for instance S = 10 allows the isolation of unreacted substrate in 98% *ee* with a quite reasonable 30% recovery.[181] In contrast, high selectivity factors (S >50) afford significant amounts of enantioenriched materials (>98% *ee*, 45%

yield). However, this procedure has the limitation of having a maximum theoretical yield of 50%, which can be improved if the undesired enantiomer can be racemised or otherwise converted back to the desired one.[182] Efforts devoted to overcoming this drawback to afford compounds with the same high enantiomeric purity but with much improved yields has led to the evolution of classical kinetic resolution into dynamic kinetic resolution (DKR).

DKR combines the resolution step of kinetic resolution with an *in situ* equilibration or racemisation of the substrate enantiomers.[182] In order for the DKR to be efficient, the rate constant for the racemisation process should be greater than the rate of reaction of the slow reacting enantiomer with the chiral reagent (*e.g.* $k_{fast} >> k_{slow}$ and $k_{rac} >> k_{slow}$, Figure 1.15). This process is governed by the continuous equilibrium between the two antipodes through the racemisation of the substrate itself, thus ideally the non-reacting enantiomer is transformed into the reacting one to afford one single stereoisomer of the product with a theoretical yield of 100%.[183]

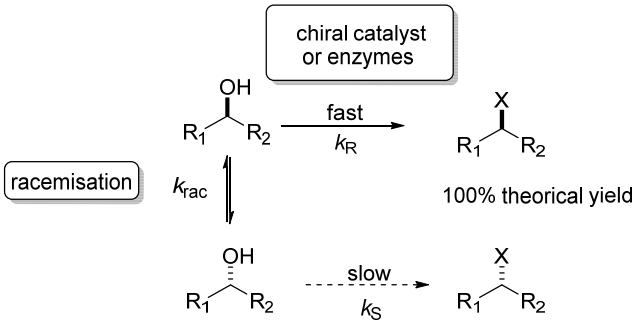


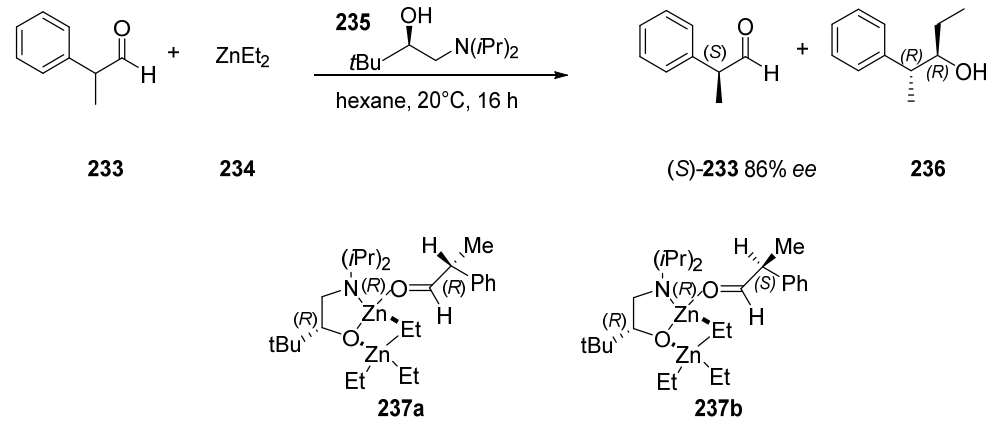
Figure 1.15 Dynamic kinetic resolution.

In contrast to KR, the levels of enantioselectivity required for DKR are lower, this means that even a modest S value of 20 allows for the preparation of product in > 90% *ee* and > 90% yield. This is due to the fact that there is no dependence of the *ee* of the product on conversion.[183]

1.6.1 Kinetic and dynamic resolution of racemic *α*-branched aldehydes

KR involving *α*-branched aldehydes remains relatively undiscovered in the scientific literature, with only a few examples involving these substrates having been reported.

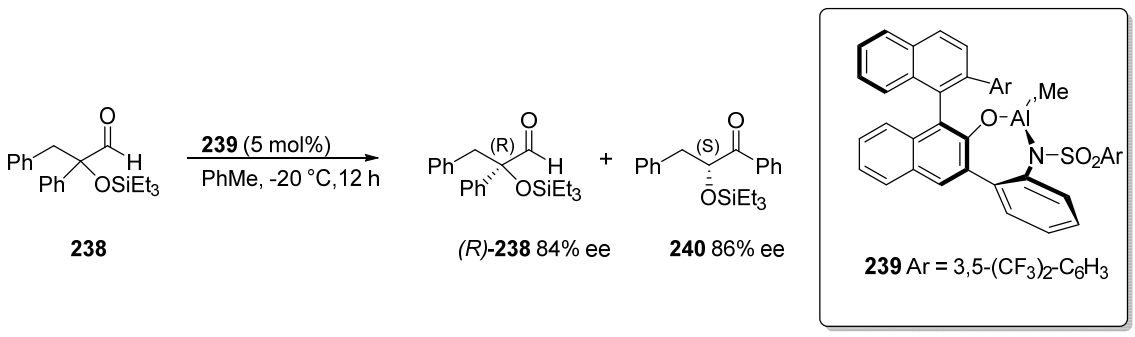
In 1991, Oguni[184] and co-workers reported the KR of α-branched aldehydes by enantioselective alkylation using diethyl zinc (**234**) with a catalytic amount of chiral β-amino alcohol **235** to furnish enantioenriched alcohol **236** (Scheme 1.56).



Scheme 1.56 KR of aldehydes by enantioselective alkylation with chiral β-amino alcohol **235**.

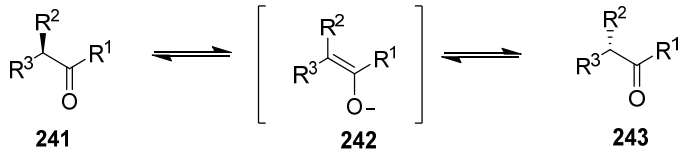
Preliminary experiments to this study showed that when (*R*)-β-amino alcohol **235** was employed, the *R* enantiomer of the racemic aldehyde **233** reacted faster than the *S*, thus the *S*-enriched aldehyde could be recovered unchanged. The enantioselective ethylation proceeds *via* a dinuclear zinc complex **237a**, in which the ethyl group attacks from the less hindered side of the carbonyl group, forming a stereocentre with *R* configuration.

In 2006 Maruoka and co-workers found that axially chiral organoaluminium Lewis acid **239** could promote an asymmetric 1,2-rearrangement of α,α-disubstituted α-siloxy aldehyde **238** under mild conditions to form enantiomerically enriched chiral α-siloxy ketones **240**, while kinetically resolving the starting aldehyde **238** (Scheme 1.57).[185]



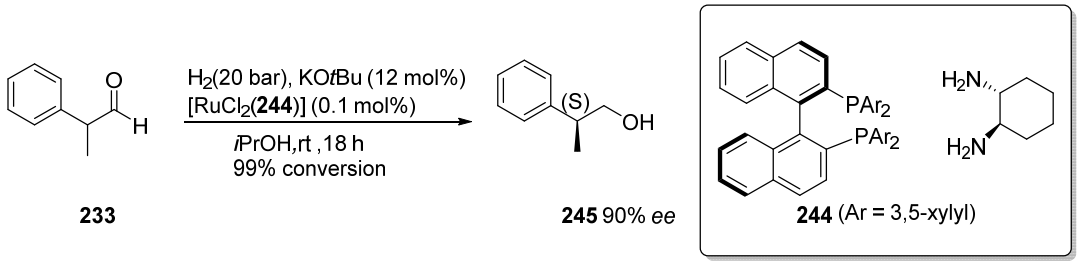
Scheme 1.57 KR of α-siloxy aldehydes using a chiral Lewis acid **239** with concomitant acyloin formation.

Alternatively, dynamic kinetic resolution of α-branched aldehydes of general type **241** has been widely investigated, presumably due to their facile racemisation to **243** under acidic or basic conditions *via* the enolate intermediate **242** as depicted in Scheme 1.58.[186]



Scheme 1.58 Racemisation *via* tautomerisation.

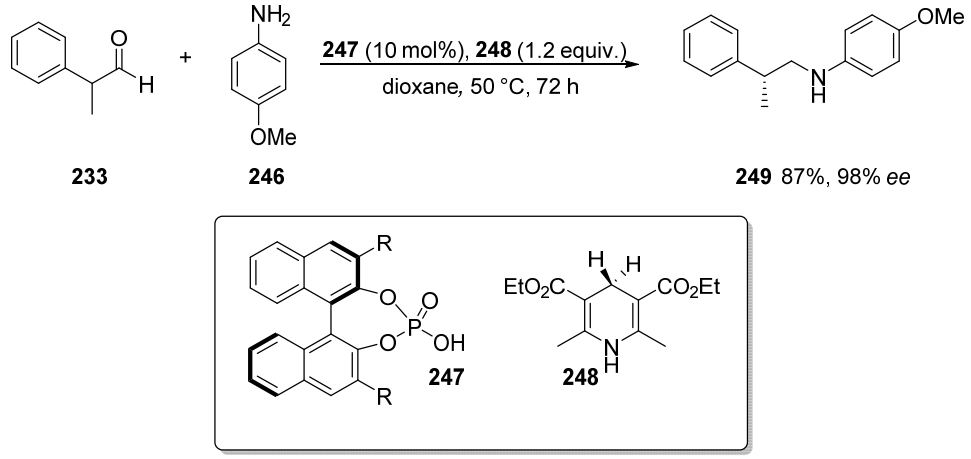
In 2007, a prime example of α-branched aldehyde DKR was reported by List and co-workers,[187] who showed that racemic α-arylaldehydes (*e.g.* **233**) could provide the corresponding primary alcohols (*e.g.* **245**) *via* dynamic kinetic resolution in excellent enantioselectivities and yields upon hydrogenation, promoted by Noyori ruthenium catalyst **244** (Scheme 1.59).[188]



Scheme 1.59 DKR of **233** by hydrogenation using Noyori Ruthenium catalyst.

Around the same time, Zhou[188] published the same reaction carried out using a similar approach, with 50 atm of H_2 and a spirocyclic diphosphine ligand. The (*S*) enantiomer **245** was furnished in 78% *ee* from **233**.

List and co-workers also described the DKR of **233** in an asymmetric reductive amination reaction with *p*-anisidine (**246**) to give α-branched amine **249** in good yield and excellent enantiomeric excess. Under the conditions depicted in Scheme 1.60, the *R*-branched aldehyde undergoes rapid racemisation in the presence of Hantzsch ester **248** (an organic hydride source) and Brønsted acid catalyst **247** *via* an imine/enamine tautomerisation.[189]



Scheme 1.60 Catalytic asymmetric reductive amination of aldehydes *via* dynamic kinetic resolution.

1.7 Chiral iminophosphoranes as an emerging class of superbase catalysts

For many years cinchona alkaloid derivatives have dominated the field of bifunctional organocatalysis, being widely regarded as a privileged system for carrying out base-promoted organic transformations in an asymmetric fashion.[84] However, these catalysts have been known to fall short with respect to the scope of the pronucleophile - limited by the basicity of the quinuclidine moiety (**79**, Figure 1.16), which can lead to impractically lengthy reaction times. In recent times, a novel group of chiral base catalysts incorporating a 'superbase'moiety has emerged in response to this shortcoming. The term superbase refers to bases with pk_{BH+} values comparable to, or greater than, that of trimethylguanidine derivatives such as guanidine **250**, cyclopropenimine **251** and iminophosphorane **252**.[190, 191]

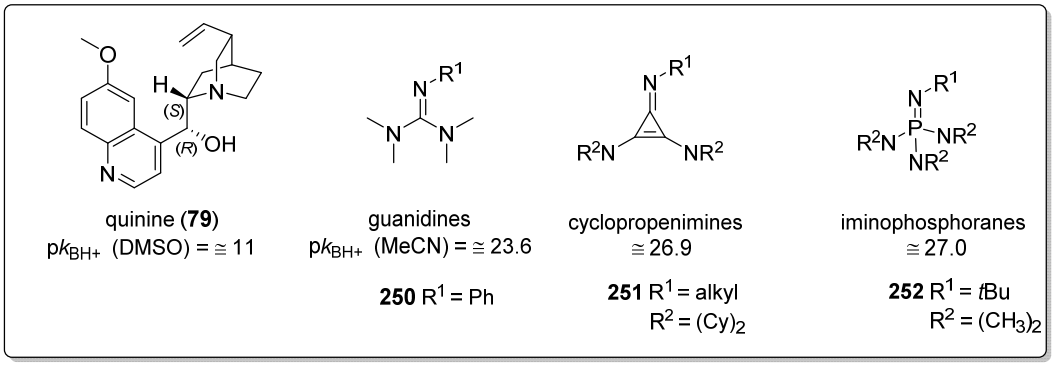


Figure 1.16 Comparison of organosuperbases and their pk_{BH+} values.

Iminophosphoranes, commonly named phosphazenes, were introduced by Schweinger in 1987[192] as iminophosphoric acid derivatives, in which the pentavalent phosphorus atom bonds to four nitrogen atoms belonging to three amines and one imine group. These compounds are much stronger bases than the well known diazabicycloundecene (DBU, pk_{BH+}(MeCN) = 24.3) or methyl-triazabicyclodecene (MTBD, pk_{BH+} (MeCN) = 25.5), and their basicity increases with the number of phosphazene units incorporated into the molecules (P_n, Figure 1.17)[193] due to more delocalisation of the positive charge in the protonated molecule. The high pk_{BH+} of these strong organic bases is directly associated with their reactivity in catalytic reactions as they are able to deprotonate a wide range of weak acids under milder reaction conditions, allowing the reaction to proceed at a higher rate. Furthermore, the use of iminophosphoranes in organocatalysis is associated with additional advantages over other organic bases, such as high solubility in nonpolar organic solvents, easy handling, low sensitivity to moisture and oxygen, and the possibility of operating at lower temperature.[193]

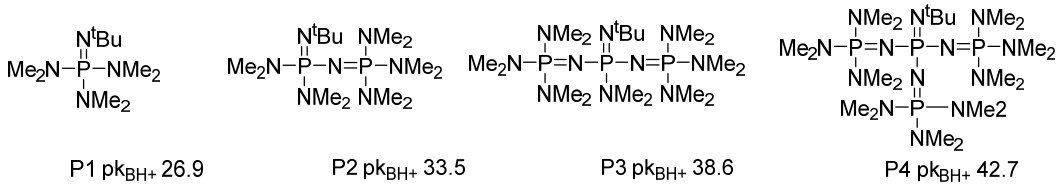


Figure 1.17 Comparison of phosphazene bases and their basicity (pk_{BH+} in MeCN).

Recognising the potential of iminophosphoranes in organocatalysis, several groups synthesised a variety of chiral iminophosphoranes, classified by three main groups based on their structural features (Figure 1.18), and demonstrated their reactivity in a variety of enantioselective transformations.

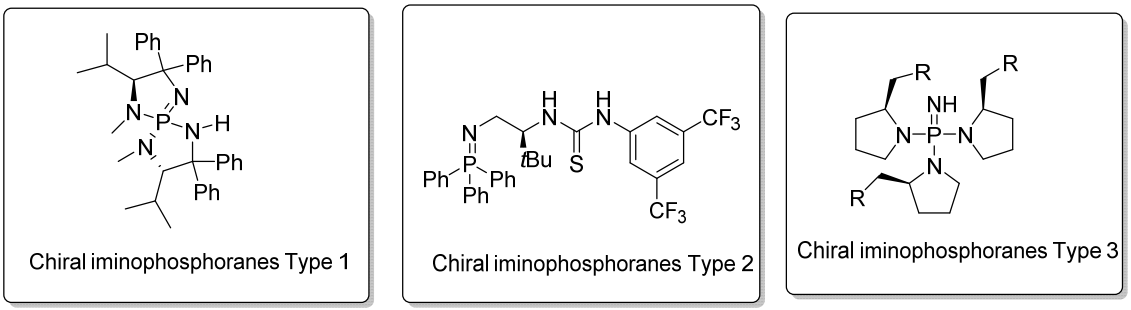
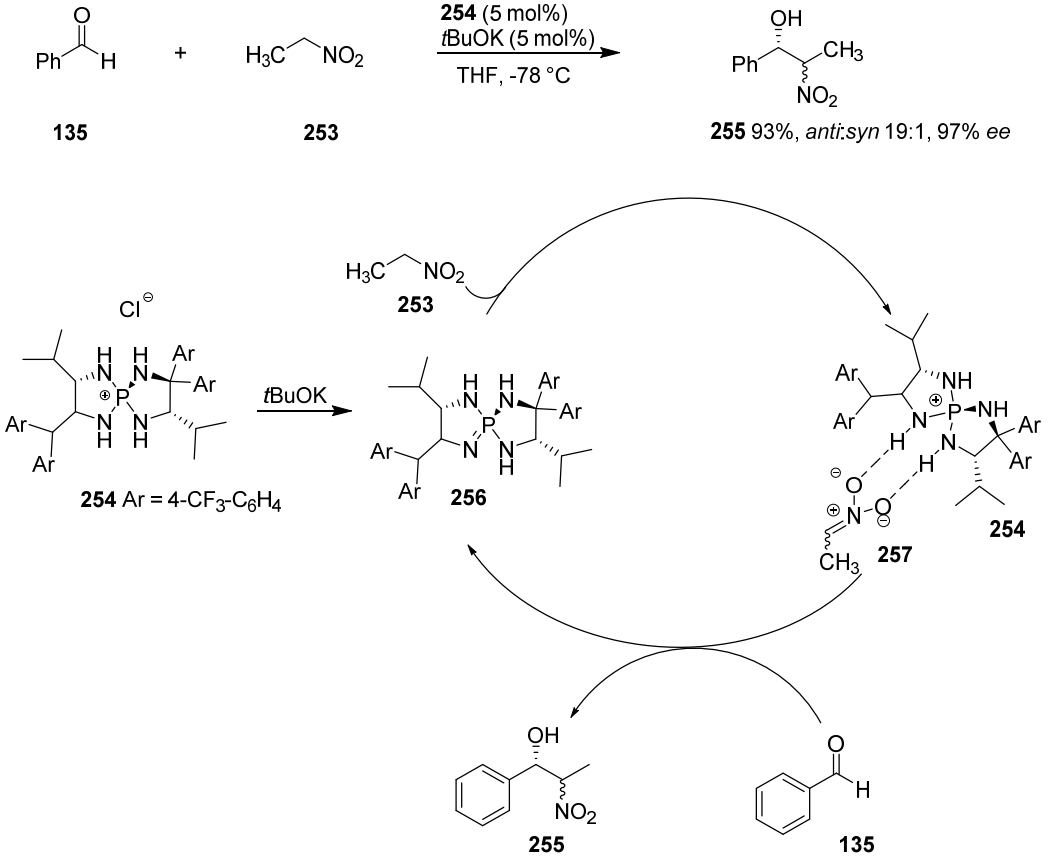


Figure 1.18 Classification of chiral iminophosphoranes.

Compounds of 'Type 1' have a general structure bearing a central phosphorus atom surrounded by a chiral spirocyclic scaffold - chirality deriving from the parent amino acid. Of this type, the [5,5]-P-spirocyclic scaffold represents the most widely explored to date. These motifs were introduced by Ooi and co-workers in 2007,[194] who synthesised them starting from a readily available L-valine derivative, a library of chiral tetraaminophosphonium salts, as potential precursors of phosphazene organocatalysts.

Initially, Henry reactions between a range of aldehydes and various nitroalkenes were used to test the efficacy of this catalyst, affording products in high yields and enantiomeric excess (Scheme 1.61).[194a]



Scheme 1.61 Henry reaction mediated by Type 1 chiral iminophosphoranes.

The authors postulated that the reaction involves intial N-H deprotonation of **254** by potassium *tert*-butoxide to furnish the active iminophosphorane catalyst **256** *in situ*, which subsequently deprotonates the nitroalkane **253** to yield nitronate anion **257**. This bidentate hydrogen-bond acceptor interacts with the phosphonium cation of **254** *via* double H-bonding, providing a chiral environment in which the highly stereoselective

addition of nitronate anion **257** to benzaldehyde (**135**) takes place, furnishing the corresponding *β*-nitroalcohol **255** with excellent diastereo- and enantiocontrol (Scheme 1.61).[194a]

In the following years, the same group developed 'free' triamino-iminophosphorane derivatives of **254** which were directly used as strong bases in a broad range of stereoselective processes such as Pudovik reactions,[195] hydrophosphonylations of aldehydes,[196] oxidations of *N*-sulfonyl imines[197] and Michael additions to nitroalkenes.[198]

Type 2 iminophosphorane organocatalysts are bifunctional systems, bearing a H-bonding moiety alongside the basic functionality, which allows for simultaneous activation of both pronucleophile and electrophile. Their structural features and mode of action will be discussed in the next Section.

In 2006, Anders and co-workers[199] reported the synthesis of a new class of chiral phosphazene bases (Type 3), possessing three (*S*)-2-(dialkylaminomethyl)-pyrrolidine units. The basicity of these systems was estimated at approximately pk_{BH+} (MeCN) = 35-37 (Figure 1.18).[199] Very recently, Suna *et al.* demonstrated that Type 3 iminophosphoranes can be obtained *via* a three-step sequential one-pot approach starting from tetraaminophosphonium tetrafluoroborates possessing an enantiomerically enriched 1,2-diamine moiety.[200] However, no information on their application as chiral bases in asymmetric synthesis has yet been reported.

1.7.1 Bifunctional iminophosphorane organocatalysis: design features and common modifications

Although Brønsted base/H-bond donor bifunctional organocatalysts have been shown to promote a wide range of enantioselective reactions,[101] they possess certain limitations such as long reaction times (even with more reactive reagents) and low catalytic activity in the presence of weak pronucleophiles and/or electrophiles. Brønsted base moieties found in traditional bifunctional organocatalysts are typically tertiary amines, with relatively low pk_{BH+} values, rendering them unable to activate less reactive pronucleophiles. In an effort to overcome these issues, Dixon *et al.*[201] developed a new class of bifunctional iminophosphorane organocatalyst (abbreviated as BIMP), possessing much stronger and more tunable Brønsted base groups capable of increasing the concentration of the nucleophilic conjugate base and therefore the rate of the

nucleophilic addition reaction with substrates of relatively low electrophilicity. In addition, by acting in synergy with an effective H-bond donor, these bases are able to render high levels of diastereo- and enantiocontrol in challenging asymmetric transformations.

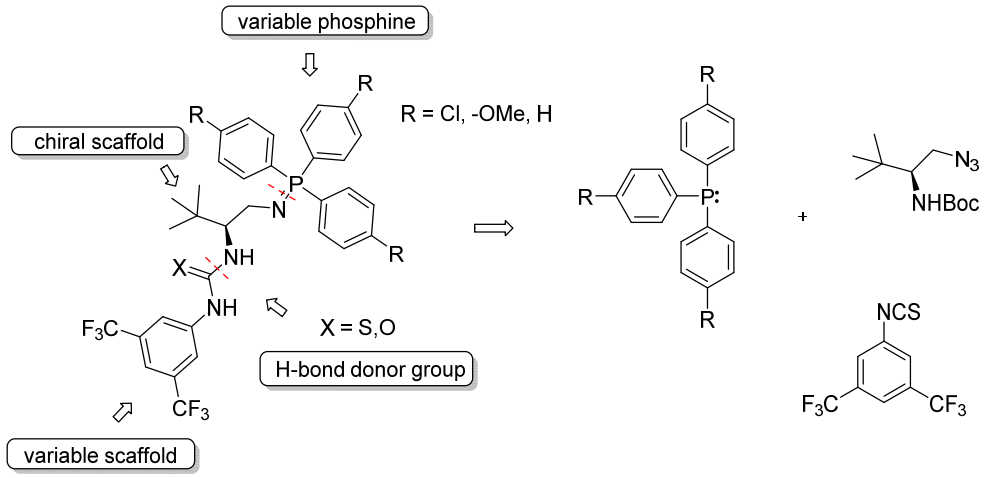


Figure 1.19 Structure elucidation and retrosynthesis of BIMP catalyst.

BIMP catalysts are easily prepared in one step *via* a Staudinger reaction between an enantiopure organoazide precursor bearing H-bond donor group and triarylphosphine (Figure 1.19). This simple synthetic approach allows steric and electronic modifications to be made at the iminophosphorane moiety by choice of substituted triarylphosphine reagents allowing for the design of catalysts with enhanced Brønsted basicity and reactivity.

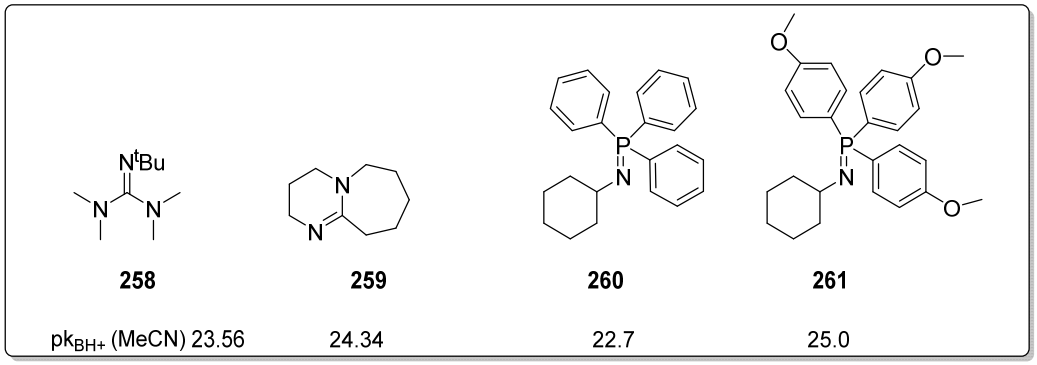


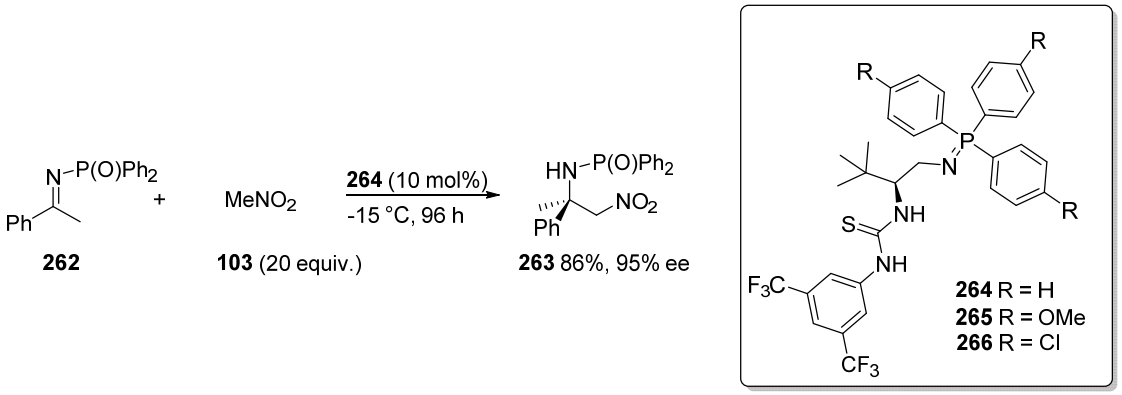
Figure 1.20 Comparison of pK_{BH+} values of TMG, DBU and iminophosphorane **260** and **261**.

For instance, comparison of the pK_{BH+} of triaryliminophosphorane derivatives **260** and **261** (in MeCN) showed **261** to be more basic than its unsubstituted counterpart, having a pK_{BH+} value of 25.0 which is comparable to other superbases such as guanidines and amidines (*e.g.* **258**, **259**). This proved that the basicity of the triarylaminophosphorane moiety can be readily modulated by varying the electronic properties of the triarylphosphine component.[202]

Further optimisation of these catalysts can also be achieved by variation of the chiral backbone scaffold, which derives from amino acids such as L-*tert*-Leucine, D-phenyl glycine, L-valine. This variable framework, coupled with a choice of H-bond donor groups including (thio)urea, amide, sulphonamide and carbamate moieties bearing stereoelectronically tunable aryl groups, provides an additional handle for optimisation. The hydrogen-bond donor substituents may also be replaced by an additional amino acid residue which can impart enhanced levels of enantiocontrol in the reactions, while maintaining excellent reactivity.[204,208]

1.7.1.1 Synthetic applications of bifunctional iminophosphorane catalysis

In 2013, the synthetic potential of this new class of bifunctional organocatalysts was investigated by Dixon and co-workers[201] in the first metal-free enantioselective nitro-Mannich reaction of nitromethane **103** with *N*-diphenylphosphinoyl ketimine **262**.



Scheme 1.62 Bifunctional iminophosphorane-catalysed asymmetric nitro-Mannich reaction of *N*-diphenylphosphinoyl ketimines.

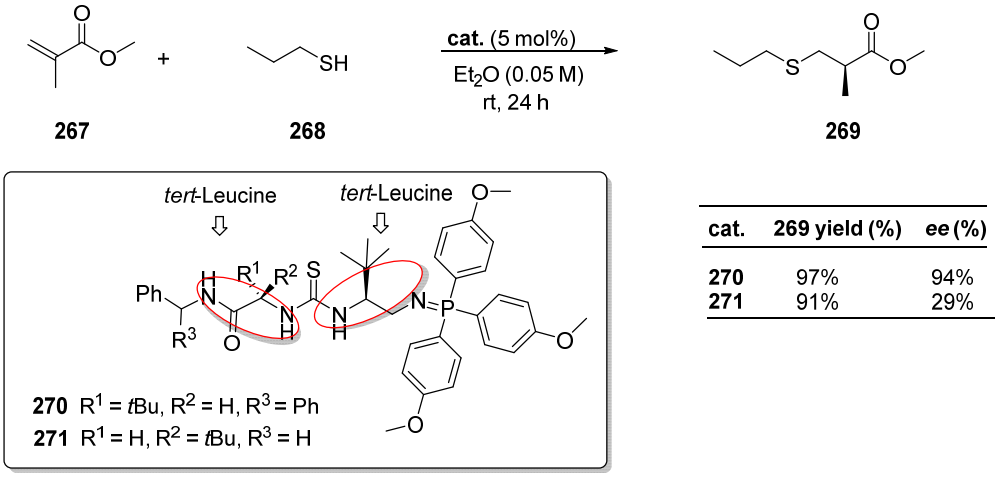
This transformation remained unexplored for years, due mainly to the low electrophilicity of ketimines and the difficulties associated with poor catalyst-substrate activation and enantiofacial discrimination which generally makes necessary the use of metal ion

catalysts, stoichiometric additives or the use of activated ketimines.[202]An evaluation of a library of BIMP catalysts synthesised from chiral azide precursors containing amino acid residues and various triarylphosphines revealed catalyst **264** to be superior, exhibiting excellent catalytic activity and furnishing the desired product **263** in good yield and excellent enantiomeric excess under optimised conditions (Scheme 1.62).[202] It is noteworthy that the reaction rate is directly correlated to the electronic effect of aryl substituents of the iminophosphorane moiety. For instance, the reaction promoted by catalyst **266** was far slower than that catalysed by either **264** or **265** (Scheme 1.62), due to the electron deficient triarylphosphine which renders the iminophosphorane nitrogen less basic. As evidence for this, the authors conducted the reaction in the presence of the cinchonine-derived bifunctional organocatalyst **100** and observed that the catalyst failed to promote the reaction even after prolonged periods of time. This result further confirmed that the enhanced basicity of iminophosphoranes compared to traditional tertiary amines is responsible for the increase in catalytic activity.[203]

Based on these studies, the same group demonstrated that the asymmetric Mannich reaction involving *N*-diphenylphosphinoyl ketimine **262** can be extended to diethyl phosphite in the presence of catalyst **265**, which delivers the respective product in excellent yield and moderate enantiomeric excess.[203]

BIMP organosuperbases were also employed in a Michael addition of aliphatic thiols to unactivated α-substituted acrylate esters (Scheme 1.63).[204] Despite this transformation being synthetically useful for the asymmetric construction of chiral sulphides,[205] no catalytic enantioselective metal-free version of had been reported previously.[206]

Catalyst **270**, obtained by introduction of an additional amino acid residue (L-*tert*-Leucine) next to the H-bond donor promoted the Michael addition of propanethiol **268** to methyl methacrylate **267** smoothly, providing enantioriched product **269** in excellent yield under optimised conditions (Scheme 1.63).[206] Both stereocentres were found to contribute to the enantiocontrol in the formation of product **269**, however, experiments carried out with catalyst **271** demonstrated that the stereogenic centres within the amide/thiourea substituent were less influential on enantiofacial control than the stereogenic centres proximal to the iminophosphorane, as both catalysts led to the formation of the desired product with the same absolute configuration (Scheme 1.63).[206]

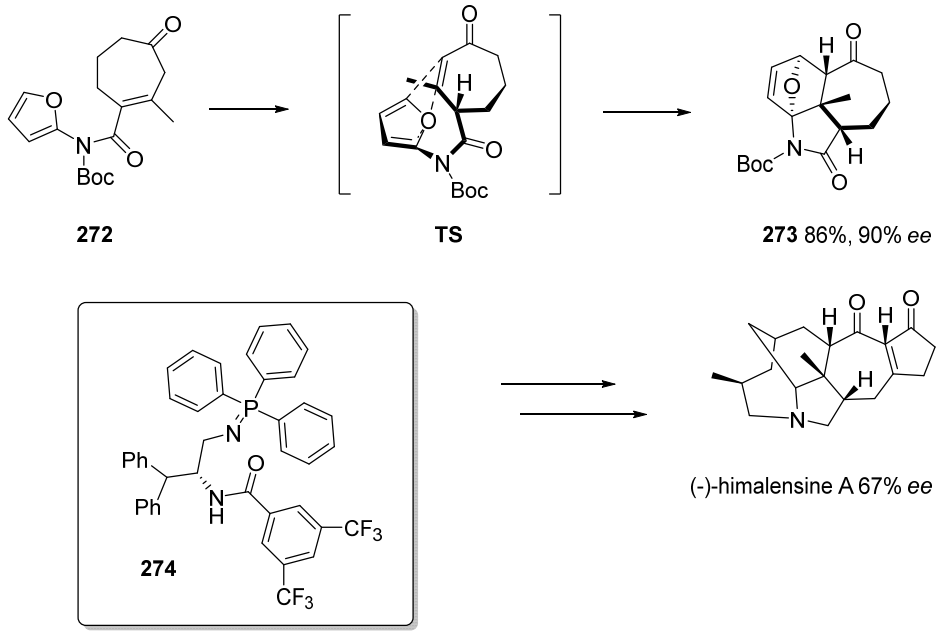


cat.	269 yield (%)	ee (%)
270	97%	94%
271	91%	29%

Scheme 1.63 Enantioselective sulfa-Michael addition to α-substituted acrylate esters promoted by iminophosphorane organocatalysts.

Very recently, a catalyst analogous to **270** possessing a phenylglycine on the iminophosphorane scaffold and a *tert*-leucine residue on the amide-thiourea *motif* as found to efficiently promote the asymmetric Michael reaction of alkyl thiols to various β-substituted-α,β-substituted-unsaturated esters with high levels of activity and enantioselectivity across a range of linear, branched, cyclic alkyl and benzylic thiols.[207] An immobilised variant of this bifunctional iminophosphorane superbase catalyst was also developed and employed in the conjugate addition of substituted malonates to nitrostyrenes.[208]

In 2017, application of an iminophosphorane derived catalyst was demonstated in the first enantioselective total synthesis of natural product (−)-himalensine.[209] Catalyst **274** was able to promote the enantioselective prototropic shift/IMDAF (furan Diels-Alder) cascade reaction of **272** which allowed the construction of the three fused ring system **273** as a precursor of (−)-himalensine in 86% yield and 90% *ee* (Scheme 1.64).[210]



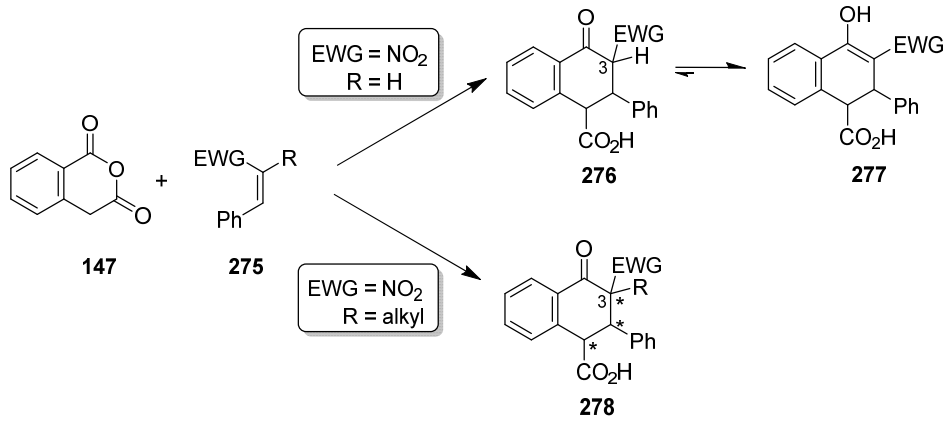
Scheme 1.64 Application of iminophosphorane catalyst in total synthesis of (-)-himalensine.

Results and discussion

2. The asymmetric organocatalytic formal cycloaddition of homophthalic anhydrides to Michael acceptors

As mentioned previously (Section 1.5.5), in recent times the Connon group has been focused on the development of the first catalytic asymmetric Tamura cycloaddition reactions between enolisable anhydrides and various Michael acceptors as electrophiles.[178,179] The results of these studies represent a promising starting point for subsequent optimisation and scope expansion studies involving different electrophiles.

Preliminary investigations carried out within our group into the catalytic asymmetric cycloaddition of homophthalic anhydride (**147**) with trisubstituted nitroalkenes **275** highlighted that *α*-alkyl substituents are required to prevent product enolisation (**277**), as the non *α*-substituted products possess a highly acidic proton at the C-3 position (**276**, Scheme 2.1). This substitution was also found to improve the rate, yield and the stereoselectivity of the reaction, and also introduces a valuable quarternary stereocentre (*e.g.* **278**).

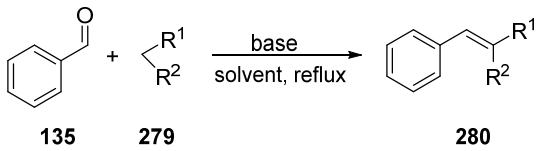


Scheme 2.1 Rationale for electrophile design.

To exploit these findings and to expand the scope of the electrophilic component in this reaction, we set about the synthesis and evaluation of substituted *α*,*β*-unsaturated carbonyl compounds as Michael acceptors.

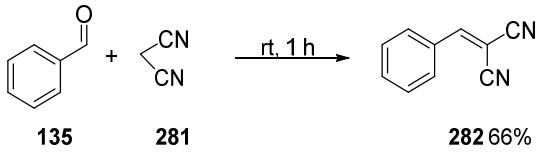
2.1 Synthesis of Michael acceptors

The synthesis of Michael acceptors was accomplished by following a general procedure based on the Knoevenagel condensation between benzaldehyde (**135**) and the appropriate substituted alkane **279** in the presence of a catalytic amount of base to furnish the respective trisubstituted alkenes **280** (Scheme 2.2).



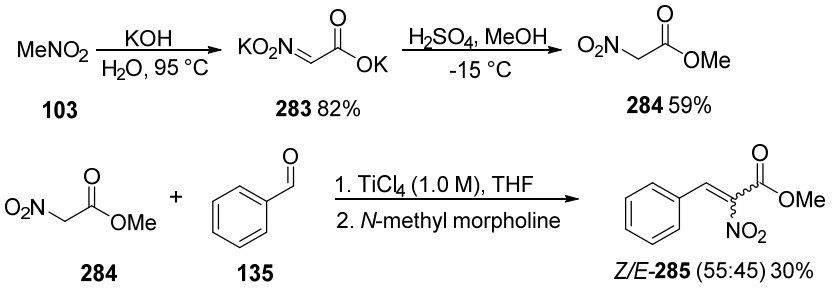
Scheme 2.2 General procedure for the synthesis of Michael acceptors.

The substrate **282** was formed in 66% yield in the reaction between benzaldehyde (**135**) and malonitrile (**281**) within 1 h at room temperature (Scheme 2.3).[211]



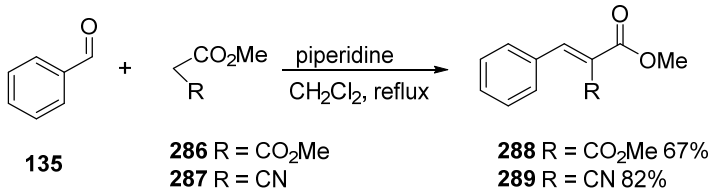
Scheme 2.3 Synthesis of substrate **282**.

The nitroalkene **285** was produced by a three step synthetic sequence: first adding nitromethane dropwise to an aqueous solution of potassium hydroxide at 70 °C under an air atmosphere. Upon cooling, the resulting salt **283** was filtered, then dissolved in methanol and treated with H_2SO_4 at -15 °C for 1 h. The isolated methyl nitroacetate **284** underwent a Knoevenagel reaction with benzaldehyde **135** in the presence of $TiCl_4$ and a catalytic amount of *N*-methylmorpholine to afford the product **285** as an inseparable mixture of *E/Z* isomers in 30% yield (Scheme 2.4).[212,213]



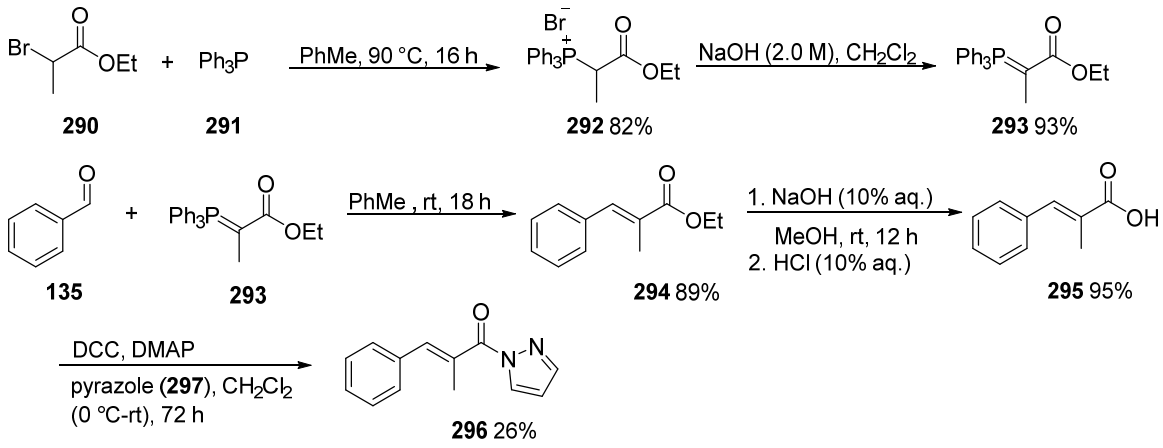
Scheme 2.4 Synthesis of the substrate **285**.

The synthesis of **288** was achieved by reacting an equimolar solution of benzaldehyde (**135**) and dimethylmalonate (**286**) in toluene at reflux in the presence of a catalytic amounts of piperidine. Purification by flash column chromatography afforded the product **288** in 67% yield. A similar procedure was followed to provide the substrate **289** from **287**. In this case the product was purified by recrystallisation from diethyl ether in excellent yield (Scheme 2.5).[214]



Scheme 2.5 Synthesis of substrate **288** and **289**

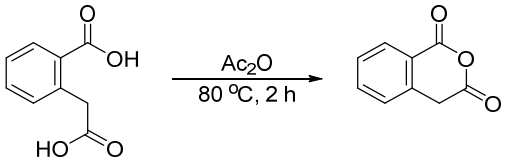
The substrate **296** was synthesised starting from the preparation of the phosphonium salt **292** by reaction of ethyl 2-bromopropionate (**290**) with triphenylphosphine (**291**). The salt **292**, once isolated, was then treated with an aqueous solution of sodium hydroxide (2.0 M) to furnish ylide **293**. This underwent a Wittig reaction with benzaldehyde to give **294**, which after hydrolysis to the acid **295** and coupling with pyrazole (**297**) in presence of DCC and a catalytic amount of DMAP delivered the desired product **296** in 17% overall yield (Scheme 2.6).



Scheme 2.6 Synthesis of **296**.

2.2 Evaluation of Michael acceptors

To test the feasibility of these electrophiles in the Tamura cycloaddition, we initially evaluated them in the reaction with homophthalic anhydride (**147**), which was prepared from readily available homophthalic acid (**298**) and acetic anhydride (Scheme 2.8). The reactions were carried out in presence of 5 mol% of catalyst **200** with an equimolar amount of **147** and the relative Michael acceptor (**280**) in MTBE (0.1 M) at room temperature (Table 2.1). These conditions were selected as they were found to be optimal in both preceding studies involving anhydrides and aldehydes.

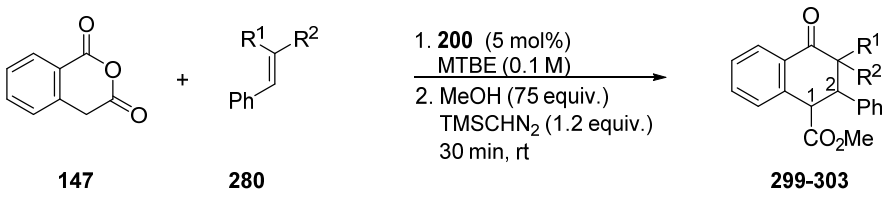


298 **147** 85%

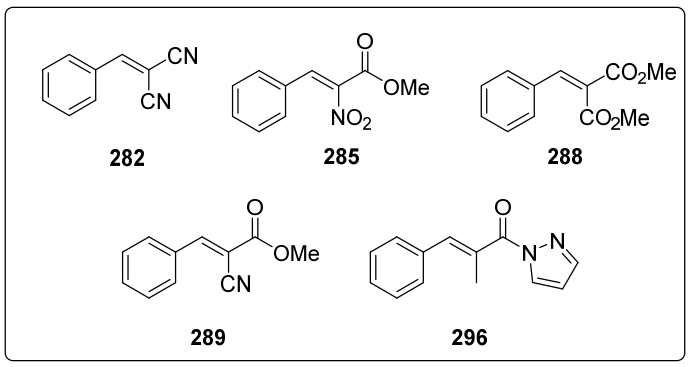
Scheme 0.8 Synthesis of homophthalic anhydride (**147**).

The results of these preliminary experiments showed that both the derivatives of malonitrile (*e.g.* **282**, entry 1) and dimethyl malonate (**288**, entry 2) failed to react, along with **296** (entry 3). Substrate **289** on the other hand reacted efficiently, providing **302** in 62% yield (entry 4). This reaction underwent a catalyst screening and optimisation process which will be discussed later (see Section 2.2.1).

Table 2.1 Preliminary evaluation of Michael acceptors as substrates.



147 **280** **299-303**



282 **285** **288**

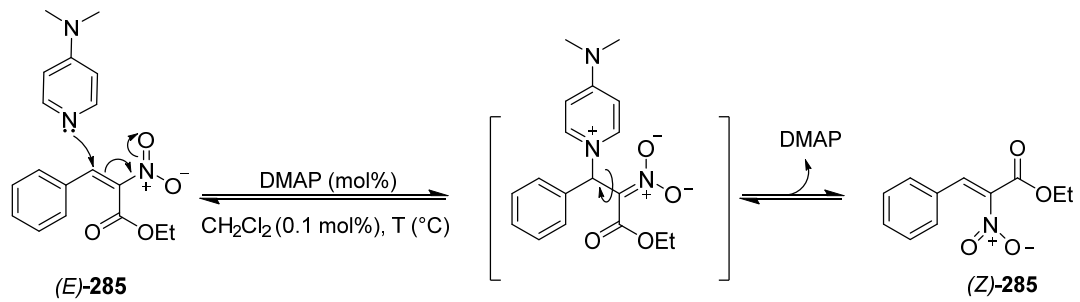
289 **296**

entry	substrate	time	product	yield (%)[a]
1	**282**	87	**299**	0
2	**288**	120	**300**	0
3	**296**	90	**301**	0
4	**289**	96	**302**	62
5	**285**	72	**303**	53

[a]Determined by ^{1}H NMR spectroscopic analysis using *p*-iodoanisole as an internal standard.

When phenyl methyl nitroacetate (**285**), existing as a mixture of two diasteroisomers *Z*:*E* = 55:45, was evaluated, the reaction proceeded to afford the product **303** in moderate yield after 72 h (entry 5). Although the reaction could result in the formation of up to four diastereomers, only one was formed in sufficient amounts to be detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. The product was found to be of *trans* geometry between H-1 and H-2, as the coupling constants measured in the ^{1}H NMR spectrum of the compound were 12.1 Hz. By serendipity, during its synthesis, (*E*)-**285** precipitated out of a solution, thus we were later able to perform an experiment with the isolated *E*-nitro olefin. Interestingly, this failed to react - suggesting that only the *Z* isomer is reactive. Without being able to isolate the *Z* isomer by conventional purification methods, we embarked on an attempt to completely isomerise the mixture to the *Z* isomer by way of a DMAP-catalysed process (Table 2.2). As shown in Table 2.2, when DMAP was employed in at 5 mol% loading, limited isomerisation of (*E*)-**285** to its *Z* isomer was observed by NMR spectroscopic analysis of the reaction mixture (entry 1, Table 2.2). After 24 hours, no improvements in the ratio were observed, therefore an extra 5 mol% of DMAP was added, which formed **285** in 28:72 *E:Z* (entry 2, Table 2.2).

Table 2.2 DMAP-promoted isomerisation process.

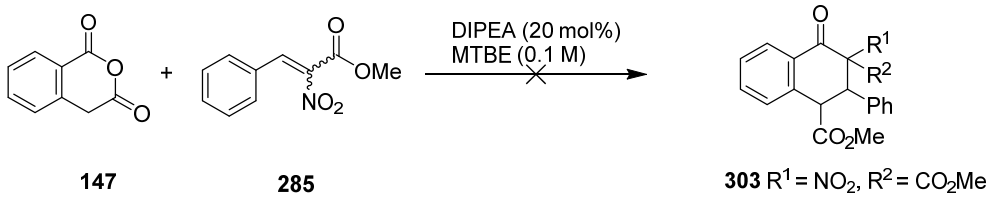


entry	DMAP (mol%)	time	T (°C)	ratio (*E*:*Z*)[a]
1	5	24	rt	33:67
2	10	24	rt	28:72
3	20	24	40	17:83

[a]Determined by ^{1}H NMR spectroscopic analysis using *p*-iodoanisole as an internal standard.

Encouraged by this observation, a further 10 mol% of DMAP (total 20 mol%) was added, providing an *E:Z* ratio of 83:17, which to our dismay could not be improved upon, even when the reaction mixture was heated at reflux temperature.

Further difficulties were encountered with this process during the racemic preparation of **303**. Following a general methodology we allowed **285** to react with homophthalic anhydride in the presence of 20 mol% Hünig's base (*i*-Pr$_2$NEt) in MTBE (0.1 M) for 24 h at room temperature. This reaction failed to furnish the product even after the addition of a stoichiometric amount *N*,*N bis*-3,5 trifluoromethyl phenylurea, leading us to abandon the investigation involving substrate **285** (Scheme 2.4).



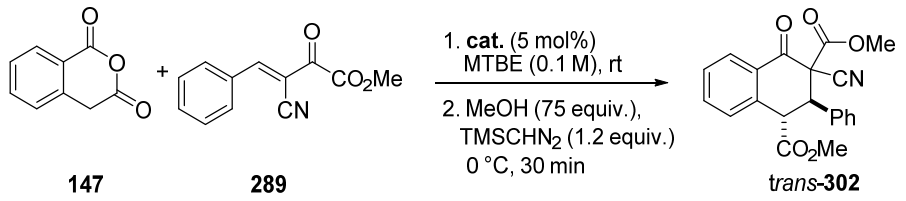
Scheme 2.4 Synthesis of racemic product **303**.

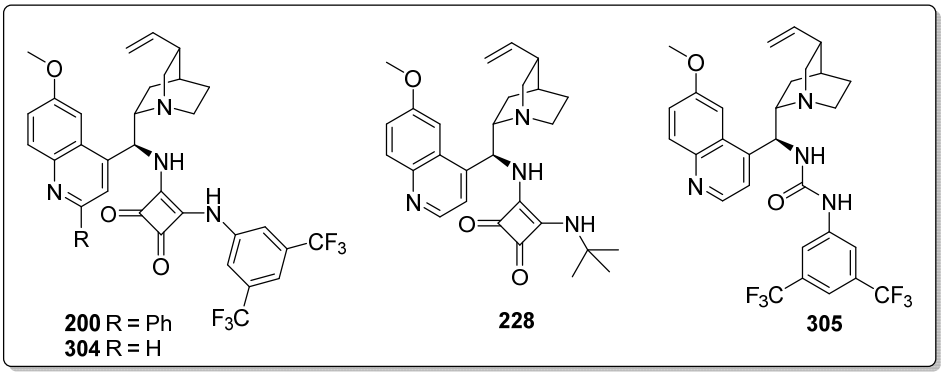
2.2.1 Evaluation of Michael acceptors of general type 289

As previously reported in Table 2.1, substrate **289** was found to react with anhydride **147** (entry 4, Table 2.1) in the presence of catalyst **200**, forming the carboxylic acid product as a single diastereomer, which was then converted to its methyl ester derivative **302** *in situ* using anhydrous MeOH, followed by TMSCHN$_2$ - for CSP-HPLC analysis. A racemic synthesis was then carried out by reaction of homophthalic anhydride and electrophile **289** in the presence of 20 mol% of DIPEA in THF at room temperature. The enantioselectivity of the process was then determined by analysing the enantiomeric excess of the isolated diastereomer by CSP-HPLC, furnishing **302** in 2% *ee* (entry 1, Table 2.3). In order to improve the stereoselectivity of this process, we turned our

attention to an evaluation of catalysts – a small library of which was available having been synthesised within the group previously.

Table 2.3 Catalyst and temperature evaluation in the cycloaddition reaction between **147** and **289**





entry	cat.	conc. (M)	T (°C)	time (h)	yield (%)[a]	ee_{trans} (%)[b]
1	**200**	0.1	rt	96	62	2
2	**304**	0.1	rt	96	64	1
3	**228**	0.1	rt	190	32	2
4	**305**	0.1	rt	96	70	1
5	-	0.1	rt	18	60	-
6	-	0.1	-30	18	44	-
7	-	0.05	rt	18	62	-

[a]Determined by ^{1}H-NMR spectroscopic analysis using *p*-iodoanisole as an internal standard. [b]ee_{trans} determined by CSP-HPLC.

All catalysts proved to possess similar activity and selectivity profiles; as product **302** was formed with moderate yield and poor asymmetric induction in all cases (entries 1-4). This led us to believe there may be a background reaction taking place in the absence

of catalyst. This proved to be the case, as without catalyst the reaction proceeded to 60% conversion in 18 h (entry 5). In attempts to suppress the background reaction we reduced the temperature of the system (entry 6) and also reduced the concentration (entry 7), both of which had little effect.

2.2.1.1 The effect of temperature on the reaction between homophthalic anhydride and 289

Unsatisfactory results from our initial catalyst screen led us to investigate the effect of reaction temperature on stereoselectivity. The reactions reported in entries 1-6 of Table 2.4 were repeated at lowered temperatures, however, only a slight improvement in enantiocontrol was observed in all cases-with longer reaction times required. Moderate stereocontrol was observed at -30 °C in the presence of catalyst **304** (entry 4, Table 2.4), which furnished **302** in 30% *ee.* Meanwhile, a similar level of stereocontrol was observed forming the opposite enantiomer when catalyst **305** was employed (entry 6, Table 2.4).

Table 2.4 Temperature evaluation

entry	cat.	conc. (M)	T (°C)	time (h)	yield (%)[a]	ee_{trans} (%)[b]
1	**200**	0.1	-15	120	95	18
2	**200**	0.1	-30	96	72	17
3	**200**	0.1	-78	96	20	26
4	**304**	0.1	-30	97	70	30
5	**304**	0.1	-78	135	10	1
6	**305**	0.1	-78	168	20	-24

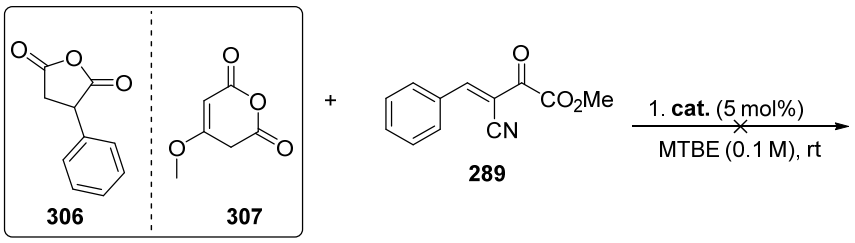
[a]Determined by ^{1}H-NMR spectroscopic analysis using *p*-iodoanisole as an internal standard. [b]ee_{trans} determined by CSP-HPLC.

2.2.2 Evaluation of the anhydride component

In a further attempt to reduce the rate of the background reaction, the use of less reactive anhydrides such as phenyl succinic anhydride (**306**) and methoxy glutaconic anhydride (**307**) were investigated. Disappointingly, both of these anhydrides gave no conversion to

their respective products after 48 hours at room temperature (entries 1-2). Heating the reactions to reflux in MTBE afforded no products after 24 hours either.

Table 2.5 Investigation of anhydrides **306** and **307**



entry	anhydride	catalyst	time (h)	yield (%)[a]
1	**306**	**200**	72	-
2	**307**	**305**	72	-

[a]Determined by ^{1}H-NMR spectroscopic analysis using *p*-iodoanisole as an internal standard.

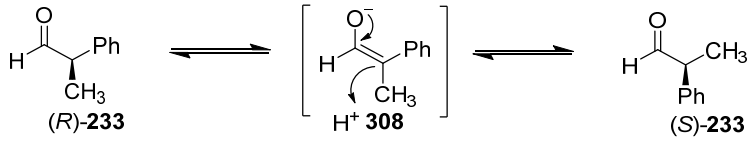
2.3 Conclusion

An attempt has been made to expand the scope of the electrophilic component in the catalytic asymmetric Tamura cycloaddition to include new activated Michael acceptors. A preliminary substrate screen identified a suitability reactive Michael acceptor, the reaction of which with homophthalic anhydride underwent a catalyst screen to enhance the stereocontrol. It was later observed that the rate of the uncatalysed background reaction was too high to achieve satisfactory levels of stereocontrol - with little suppression of which being observed on decreasing the temperature, lowering the concentration and switching to less reactive anhydrides. A failure to eliminate the background reaction meant superior levels of stereocontrol would be out of reach, leading us to abandon this project.

3. Cycloaddition reactions between homophthalic anhydride and 2-phenylpropionaldehyde

Since the recent promising results obtained from studies on the catalytic cycloaddition reaction between homophthalic anhydrides and various aldehydes[150] (Section 1.5.1), the Connon group has been involved in probing catalysts' ability to kinetically resolve *α*-branched aldehydes. At the onset of these studies two possible processes were proposed:

1) In a chiral environment (in the presence of bifunctional cinchona alkaloid derived catalyst) the cycloaddition between one of two enantiomers of a chiral aldehyde to homophthalic anhydride should proceed faster than that of the other, affording a maximum 50% yield of enantiopure dihydroisocoumarin derivatives bearing three contiguous stereocentres *via* a kinetic resolution process.
2) In the presence of a Brønsted acid/base catalyst, *α*-branched aldehydes (*e.g.* (*R*)-**233** and (*S*)-**233**) could undergo racemisation by keto-enol tautomerism (**308**, Scheme 3.1), affording a possible 100% yield of dihydroisocoumarin derivatives *via* a dynamic kinetic resolution process.



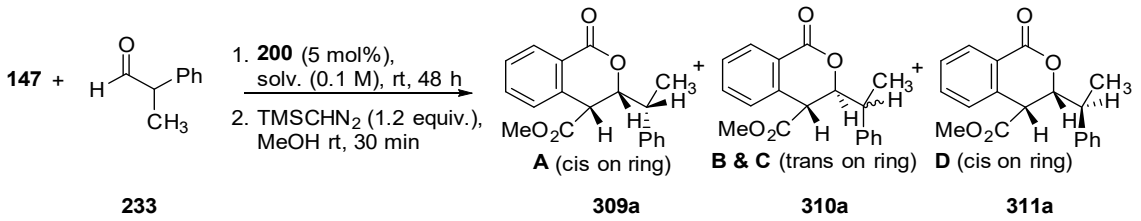
Scheme 3.1 Dynamic kinetic resolution of α-branched aldehyde **233**.

Despite both of these processes having high synthetic potential, no studies regarding kinetic and dynamic resolution of *α*-branched aldehydes promoted by bifunctional organocatalysts have been reported to date.

3.1 Preliminary experiments

To verify the plausibility of this process, we initially decided to evaluate the reaction involving equimolar amounts of **147** and **233** promoted by 5 mol% of catalyst **200** at room temperature in MTBE (0.1 M). After 48 h product yields (with respect to *p*-iodoanisole as an internal standard) and diastereomeric ratios were determined by ^{1}H NMR spectroscopic analysis of the reaction mixture. Subsequent extraction with sodium bicarbonate solution followed by acidification with hydrochloric acid solution and a second extraction with organic solvent allowed for the isolation of the lactone-acids **309**,

310 and **311**. In order to facilitate the analysis of the enantioselectivity by CSP-HPLC, the mixtures of the diastereoisomeric acids were then converted to their methyl ester derivatives by the previously described procedure and then purified by flash column chromatography on silica gel (Scheme 3.2).



Scheme 3.2 Preliminary study on aldehyde **233**.

The desired product contains three stereocentres, therefore a possible four diastereomers may be formed - named according to where their H-2 resonances arose in the ^{1}H NMR spectrum.

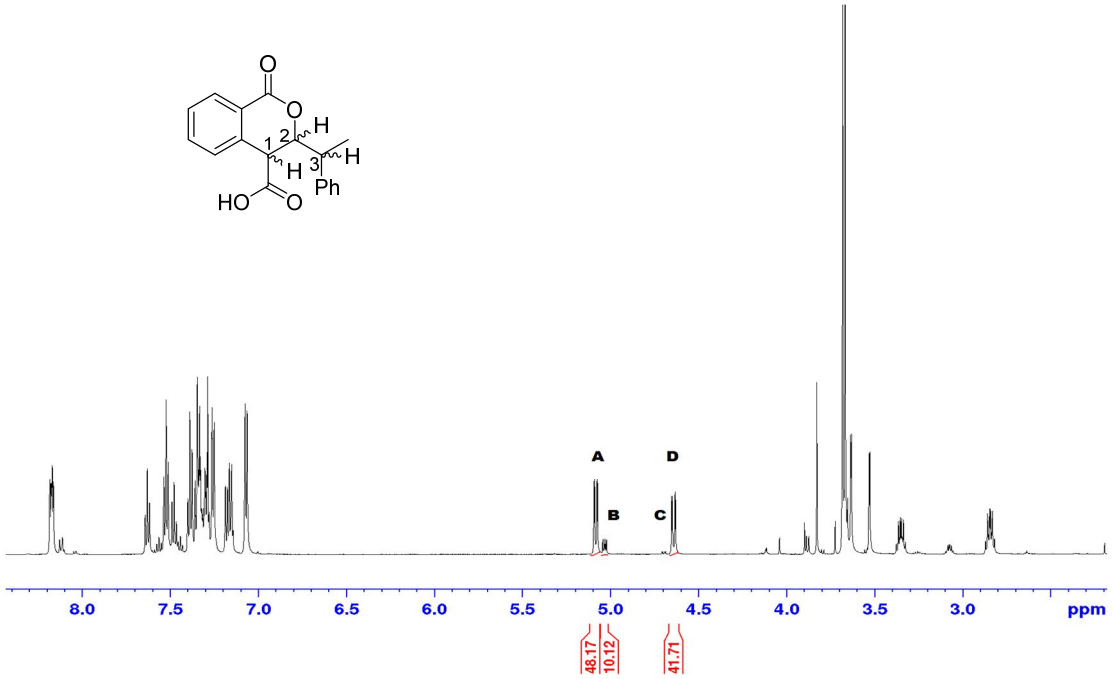


Figure 3.1 Assignment of diastereomers by^{1}H-NMR spectroscopic analysis.

As can be seen in Figure 3.1, the preliminary reaction reported above formed three diastereomers with a *dr* = 48:10:0:42, with each being formed in 99% *ee* (CSP-HPLC analysis). The relative stereochemistry of diastereomers **A** and **D** was elucidated by interpretation of coupling constants in the ^{1}H-NMR spectrum. Small *J* values were

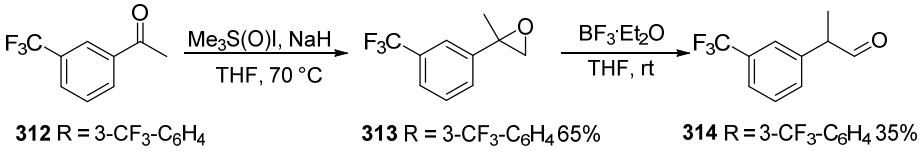
observed from (H-1) to (H-2), while large and small *J* values were observed from (H-2) to (H-3), indicating these diastereomers possess a *cis* orientation on the ring and also differ from each other based on the configuration of H-3. Meanwhile diastereomers **C** and **D** have a *trans* orientation on the ring and also differ from each other based on the configuration of the stereocentre outside of the ring. These assumptions were later confirmed by X-ray crystal structure analysis of diastereomer **D**, isolated by Dr Umar Farid.

3.2 Synthesis of *α*-branched aldehydes

With a robust screening procedure in hand, we began an investigation into the development of a protocol with improved diastereocontrol which could maintain already established levels of enantiocontrol, and if possible, improve the yield of the dihydroisocoumarin by extending the process to dynamic kinetic resolution.

We started with the synthesis and evaluation of various electron-deficient aldehydes bearing enol-stabilising electron-withdrawing groups on the aromatic ring, which could potentially promote racemisation at a faster rate than the reaction of the slower-reacting enantiomer, pushing towards efficient DKR of the aldehyde.

Synthesis of aldehyde **314** was carried out according to a known literature procedure based on the Johnson-Corey-Chaykovsky reaction (Scheme 3.3).[226] To a reaction mixture of sodium hydride and trimethylsulfoxonium iodide in THF at 70 °C was added the ketone **312**. The corresponding epoxide **313** was then isolated by column chromatography on silica gel in moderate yield and treated with BF_3•OEt to furnish the aldehyde **314**.

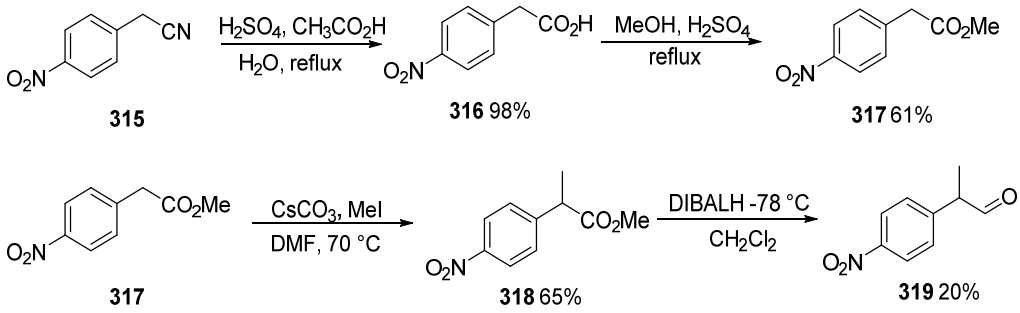


312 R = 3-CF_3-C_6H_4 **313** R = 3-CF_3-C_6H_4 65% **314** R = 3-CF_3-C_6H_4 35%

Scheme 3.3 Synthesis of aldehydes **314**.

The substrate **319** was synthesised starting from *p*-nitro phenylacetonitrile (**315**), which was converted to the corresponding acid **316** by hydrolysis with dilute sulfuric acid and acetic acid at reflux. The *p*-nitrophenyl acetic acid then underwent an esterification with methanol in presence of catalytic sulfuric acid to afford **317** in 61% yield. Subsequent alkylation of **317** was achieved using methyl iodide and caesium carbonate in DMF at

70°C to obtain the *α*-substituted methyl nitrophenyl acetate **318**. This was then reduced by DIBAL-H (solution in THF) which was added dropwise at -78 °C for an hour (Scheme 3.4).[215] After completion of the reaction, the desired product **319** was isolated after purification by column chromatography.

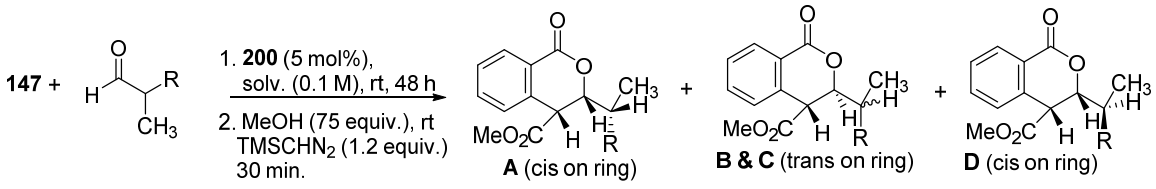


Scheme 3.4 Synthesis of aldehyde **319**.

3.3 Preliminary investigations on the DKR of aldehydes 314 and 319

Subsequent evaluation of substrates **314** and **319** was carried out under the same conditions as reported in the preliminary study (Section 3.1). Although it was observed that these reactions proceeded relatively quickly, with complete consumption of the aldehyde component after 48 h with excellent enantioselectivity, the *dr* shows that DKR could not be occurring, as the ratio between the two *cis*-diastereomers was approximately 1:1 (entries 1-2). Furthemore, hardly any change in *dr* was observed when the more acidic aldehyde was employed, meaning little to no racemisation could be taking place.

Table 3.1 Evaluation of substrates **314** and **319**



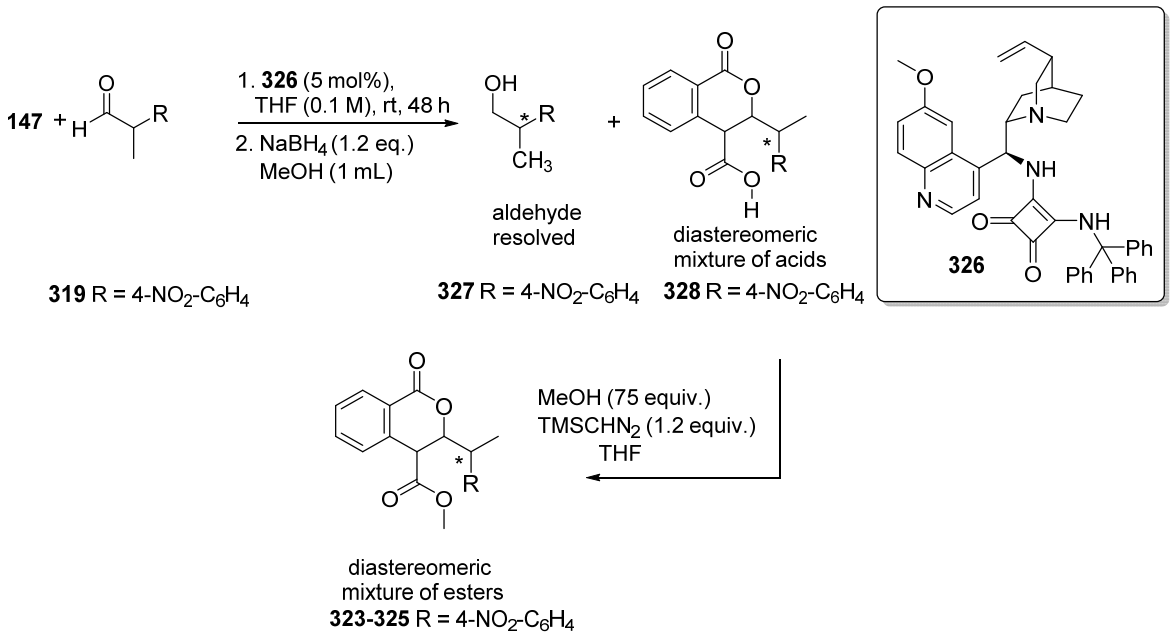
entry	cat.	substrate	solvent	yield (%)[a]	*dr* (A:B:C:D)[d]	*ee* (%) A:B:C:D[c]
1	**200**	**314**	MTBE	53	44:7:4:45	99:99:-:99
2	**200**	**319**	THF	54	38:10:6:46	99:99:-:99

[a]Isolated yield of the esterified diastereomeric mixture after flash column chromatography.[b]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis. [c]Determined by CSP-HPLC.

3.3.1 Investigations on KR of aldehyde 319

The experiment involving substrate **319** was then repeated using 0.5 equiv. of anhydride in order to investigate possible KR of the aldehyde. Once the anhydride was fully consumed, the remaining aldehyde was reduced to the corresponding alcohol **327** *in situ* using sodium borohydride (1.5 equiv.), in order to prevent any racemisation of the potentially resolved aldehyde during the aqueous base extraction employed for the isolation of the crude diastereomeric mixture **328**. Subsequent evaluation of the *ee* was possible by CSP-HPLC. Table 3.2 shows the results of these reactions along with the investigation of one additional catalyst **326** displayed below. A preliminary catalyst screen performed by Dr Umar Farid (See Appendix, page 261) suggests that the introduction of a bulky substituent such as a trityl group to the squaramide **326** could provide a level of steric hindrance around the active region of the catalyst which may enhance stereocontrol, therefore we went about employing bulkier catalysts.

Table 3.2 Investigation of the kinetic resolution of **319**

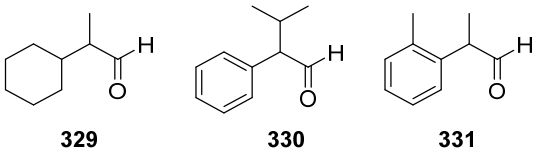


entry	cat.	solv.	T (°C)	*ee* $_{alcohol}$ (%)[a]	yield (%)[b]	*dr* (A:B:C:D)[c]	*ee* (%) A:B:C:D[a]
1	**200**	THF	rt	0	21	43:4:5:48	99:99:-:99
2	**326**	THF	-60 °C	45	23	12:7:26:55	99:99:-:99

[a]Determined by CSP-HPLC. [b]Isolated yield of the esterified diasteromeric mixture after flash column chromatography. [c]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis.

3.4 Expansion of substrate scope

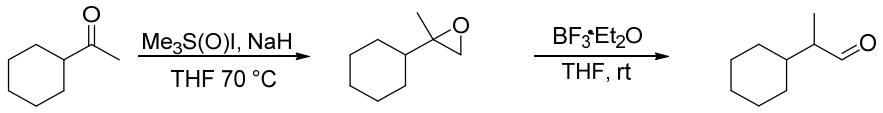
Since the previous studies showed no increase in diastereocontrol when electron-withdrawing groups were introduced to the aromatic ring of the aldehyde, we decided to investigate the influence of sterics by incorporating bulky groups into the *α*-branched aldehyde - which could potentially promote a more efficient KR. The aldehydes chosen to improve the diastereo- and enantioselectivity are shown in Figure 3.2.



329 **330** **331**

Figure 3.2 Substrates synthesised for the evaluation of the reaction scope.

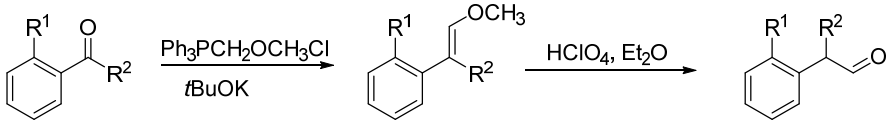
The aldehyde **329** was synthesised as per the previously reported Johnson-Corey-Chaykovsky method going *via* the epoxide **333** starting from ketone **332** (Scheme 3.5).[226]



332 **333** 30% **329** 58%

Scheme 3.5 Synthesis of aldehyde **329**.

Aldehydes **330** and **331** were synthesised by dropwise addition of ketones **334** and **335** to a solution of (methoxymethyl)triphenylphosphonium chloride and potassium *tert*-butoxide at 0 °C to afford the (*Z*/*E*)-enol-methyl ethers **336** and **337** in 35% and 45% yields respectively after purification by column chromatography. Compounds **336** and **337** were then treated with a 70% aqueous solution of perchloric acid, which furnished the corresponding *α*-arylaldehydes **330** and **331** which were isolated in low to moderate yields after column chromatography (Scheme 3.6).[216]

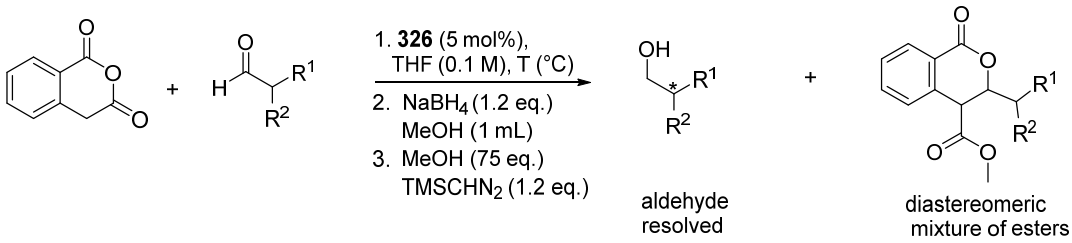


334 R^1 = H, R^2 = -CH(CH$_3$)$_2$ **336** R^1 = H, R^2 = -CH(CH$_3$)$_2$ 35% **330** R^1 = H, R^2 = -CH(CH$_3$)$_2$ 57%
335 R^1 = CH$_3$, R^2 = CH$_3$ **337** R^1 = CH$_3$, R^2 = CH$_3$ 45% **331** R^1 = CH$_3$, R^2 = CH$_3$ 35%

Scheme 3.6 Synthesis of aldehydes **330** and **331**.

To investigate whether KR of the aldehydes shown in Figure 3.2 was occurring, the reactions were performed using 0.5:1 equivalents of anhydride:aldehyde in the presence of catalyst **326**.

Table 3.3 Investigation of the KR of bulky aldehydes



147

329 R^1 = cyclohexyl, R^2 = CH_3
330 R^1 = C_6H_5, R^2 = -$CH(CH_3)_2$
331 R^1 = 2-CH_3-C_6H_4, R^2 = CH_3

338 R^1 = cyclohexyl, R^2 = CH_3
339 R^1 = C_6H_5, R^2 = -$CH(CH_3)_2$
340 R^1 = 2-CH_3-C_6H_4, R^2 = CH_3

341 R^1 = cyclohexyl, R^2 = CH_3
342 R^1 = C_6H_5, R^2 = -$CH(CH_3)_2$
343 R^1 = 2-CH_3-C_6H_4, R^2= CH_3

entry	substrate	T (°C)/time (h)	$ee_{alcohol}$ (%)[a]	yield (%)[b]	*dr* (A:B:C:D)[c]	*ee* (%) A:D[a]
1	**329**	rt/24	52	33	29:0:0:71	99:99
2	**330**	rt/24	55	51	25:0:2:73	99:99
3	**330**	-30/48	66	81	21:0:1:78	99:99
4	**331**	rt/48	53	43	11:0:3:86	99:99
5	**331**	-60/120	60	55	5:0:0:95	19:99

[a]Determined by CSP-HPLC. [b]Isolated yield of the esterified diasteromeric mixture after flash column chromatography. [c]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis.

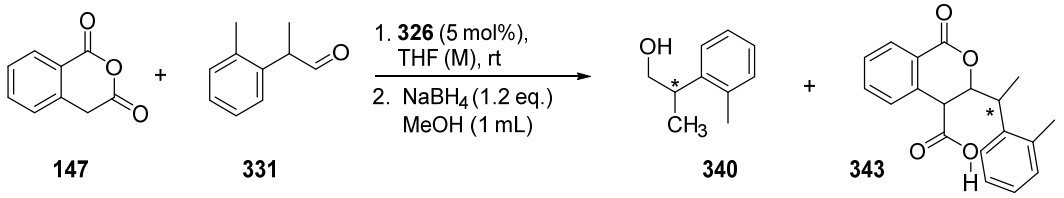
Gratifyingly, KR of the aldehydes under investigation was found to occur, with the unreacted aldehydes being present in moderate *ee* at the end of the reaction (entries 1-5). The catalyst **326** (entries 1-5) was found to promote the reaction to give **D** as the major diastereomer with excellent enantioselectivity in all cases. It appeared the introduction of a bulky substituent to the *α*-position of the aldehyde was of great benefit to the diastereocontrol of the process (entries 2 and 3). Lowering the temperature of the reaction also led to further improvements in *dr*, along with an improved resolution of the aldehyde (entry 3). It is also noteworthy that increasing the steric bulk of the aldehyde by the introduction of a methyl group to the phenyl ring also increased the formation of diastereomer **D** over **A** and **C** (entry 4), which was also observed by lowering the reaction temperature to -60 °C (entry 5). Unexpectedly, both entries 4 and 5 show a discrepancy in the observed *dr* and enantiomeric excess of the resolved aldehyde (as the theorical %*ee*

of the resolved aldehyde is supposed to be equal to the difference in the ratio 95:5 indicating that some aldehyde racemisation took place).

3.4.1 Kinetic studies involving aldehyde 331

With the aim to confirm the previous results, we embarked on a series of kinetic studies in which we monitored the diastereoselectivity of the product mixture and enantiomeric excess of the unreacted aldehyde over the time. If we assume that the process occurs by KR, we should expect that as the aldehyde reaches 50% conversion, the faster reacting enantiomer would be consumed and its concentration in solution would decrease. Meanwhile, the slower reacting enantiomer should still be present in solution in relatively high concentration, and continues to react at its own rate, causing a change in *dr* over time.

Table 3.4 Investigation into the KR of aldehyde **331**



entry	C (M)	time	$ee_{alcohol}$ (%)[a]	yield (%)[b]	*dr* (A:B:C:D)[c]	*ee* (%) A:D[a]
1	0.1	1	84	81	11:0:3:86	99:99
2	0.1	18	87	81	11:0:3:86	99:99
3	0.1	48	53	33	11:0:3:86	99:99
4	0.2	18	83	43	12:0:4:84	99:99
5	0.4	18	54	44	10:0:3:87	99:99

[a]Determined by CSP-HPLC. [b]Isolated yield of the diasteromeric mixture after flash column chromatography. [c]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis.

Thus, the experiment summarised in entry 4 of Table 3.3 was repeated and monitored over 48 h. By ^{1}H-NMR spectroscopic analysis of the crude reaction mixture we observed that after 1 h (entry 1) the conversion reaches completion as 0.5 equivalents of homophthalic anhydride was consumed. Surprisingly, the diastereoselectivity measured was found to be constant over time, while the *ee* of the unreacted aldehyde was 84% after the first 18 hours (entry 2), then decreased dramatically to 53% after 48 hours longer

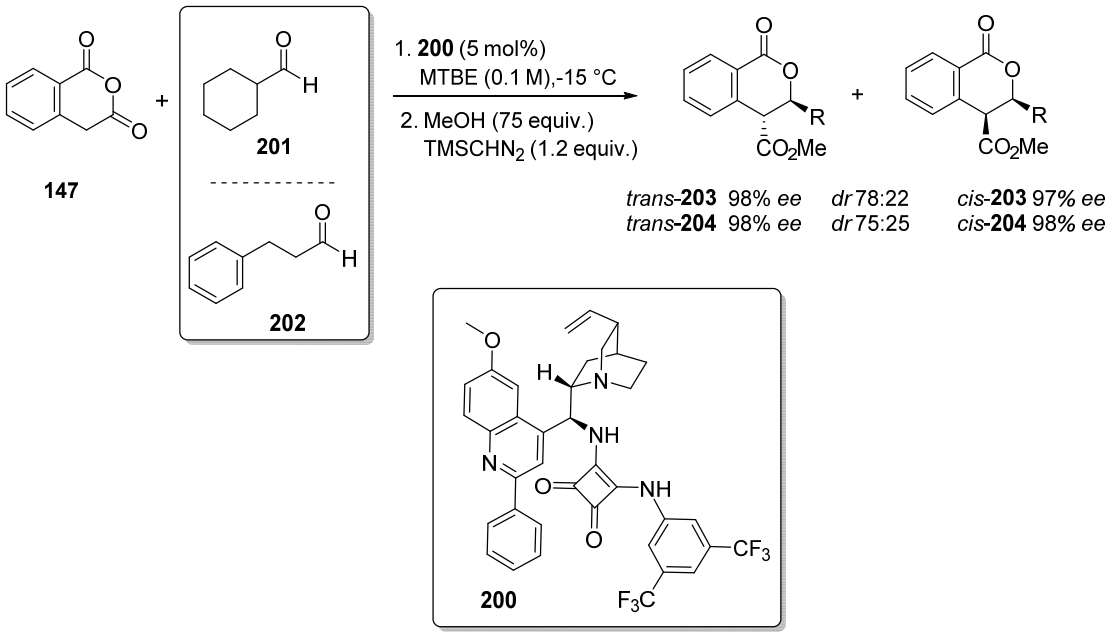
(entry 3). To explain these results we assumed the rate constants of the two enantiomers are dramatically different, allowing for the selective interaction of one of the two enantiomers with the catalyst. Moreover, changes in the *ee* of the resolved aldehyde over time might be due to its racemisation promoted by the lactone carboxylate species - which could occur when the reaction mixture is left standing after completion for an extended period of time. In order to minimise this phenomenon we repeated the same experiment under diluted solutions – to no avail (entries 4 and 5).

3.5 Conclusion

The synthesis of a novel three stereocentre-containing dihydroisocoumarin acid has been achieved with good enantio-and diastereocontrol by way of a kinetic resolution process. We have demonstrated for the first time that electron-deficient substituted α-branched aldehydes can be kinetically resolved at low temperature, and that the use of a bulky substituted squaramide catalyst provides moderate levels of stereocontrol. An investigation into the effect of the steric bulk of the aldehyde on the stereochemical outcome found that bulky α-branched aldehydes allow for a far more selective process.

4. The asymmetric organocatalytic formal cycloaddition of homophthalic anhydrides to aldehydes

As described in Sections 1.5.1 and 1.5.2, our group has recently been involved in the development of the first one-pot asymmetric cycloaddition reactions involving enolisable anhydrides and various aldehydes in the presence of an *ad hoc*-designed novel cinchona alkaloid derived organocatalyst.[150] This process is synthetically useful as it is able to furnish enantioenriched 3,4-dihydroisocoumarin and *γ*-butyrolactone compounds which are simple derivatives of a class of natural products of considerable pharmacological activity.[152-157,162-164] During these studies, a screening of different aldehydes under optimised conditions highlighted that when hindered 'branched'or aliphatic straight-chain aldehydes (*e.g.* **201**, **202**) were employed, higher levels of the *cis*-diastereomer (*e.g.* **203** and **204** respectively) could be obtained than when aromatic aldehydes were used (Scheme 4.1).



Scheme 4.1 Catalytic cycloaddition reactions between homophthalic anhydride and aliphatic aldehydes.

Inspired by this observation, we decided to investigate the possibility of reversing the *trans* favoured diastereoselectivity previously observed, *via* catalyst design and choice of aliphatic aldehyde, in order to provide one pot access to functionalised *cis* products

(which are well known for their moderate antibacterial and antifungal activities – see Section 1.5.4).[175]

4.1 Catalyst evaluation in the formal cycloaddition reaction between homophthalic anhydride and hydrocinnamaldehyde

We first focused on the evaluation of a relatively large library of cinchona-based organocatalysts as reaction promoters. Most of these catalysts had been previously synthesised by fellow researchers within the group for the development of various other asymmetric transformations. For this reason, it was possible to evaluate a wide range of structures and compare their catalytic performance in the reaction between homophthalic anhydride (**147**) and hydrocinnamaldehyde (**202**). Catalyst structures which were employed are depicted in Figure 4.1, while the results of their evaluation are reported in Table 4.1.

The protocol we used involved the reaction of equimolar amounts of **147** and **202** promoted by 5 mol% of catalyst at -15 °C in MTBE (0.1 M). We chose these conditions as they were found to be optimal in the preceding studies involving anhydrides and aldehydes. After 24 h product yields were determined by ^{1}H NMR spectroscopic analysis of the crude using *p*-iodoanisole as an internal standard, and the diastereoselectivity of the reactions was quantified. Following the standard procedure described in previous Sections, the mixtures of the lactone-acids were esterified and purified by column chromatography to obtain diastereomeric mixtures of esters **204**- the enantiomeric excess of which could be determined by CSP-HPLC analysis.

Various bifunctional catalysts bearing different hydrogen-bond donating moieties were evaluated and in all cases we observed good product yields and reasonable reaction times. *N*-aryl-(thio)urea-cinchona derived catalysts **305** and **106** exhibited similar catalytic profiles, as they both furnished a mixture of *trans* and *cis* acid-lactones in a ratio of ~ 2:1 with poor to moderate enantiocontrol (entries 1 and 3) - which increased for both diastereomers in the presence of the trityl *N*-urea derivative catalyst **344** (entry 2). Sulfonamide cinchona-derived catalysts **345** and **346** (kindly provided by Mr Romain Claveau) were also employed, however no improvements in *cis*-diastereo- and enantiocontrol were observed (entries 4-5). In order to explore the catalytic performance of systems bearing a different dual hydrogen-bond donating moiety at the C-9 position,

we decided to evaluate squaramide-substituted cinchona alkaloids. Catalyst **304** (entry 6) was evaluated and compared to its analogue **200** bearing a phenyl ring in the C-2' position (entry 7). Contrary to previous observations (Sections 1.5.1 and 1.5.2) in which substitution at the C-2' position improves the catalytic performance, we observed that its absence led to slightly improved levels of the *cis*-diastereomer over the *trans.*

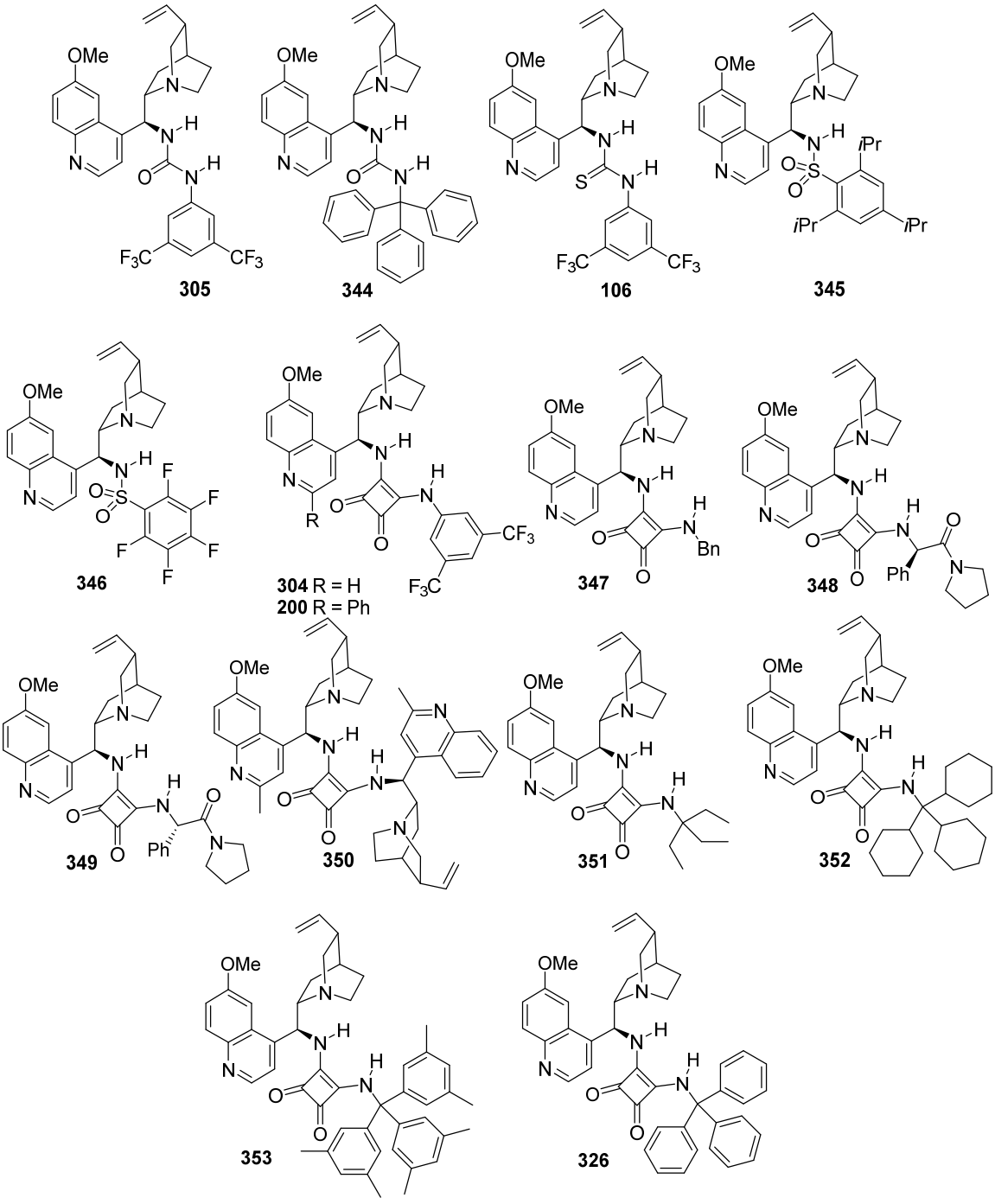
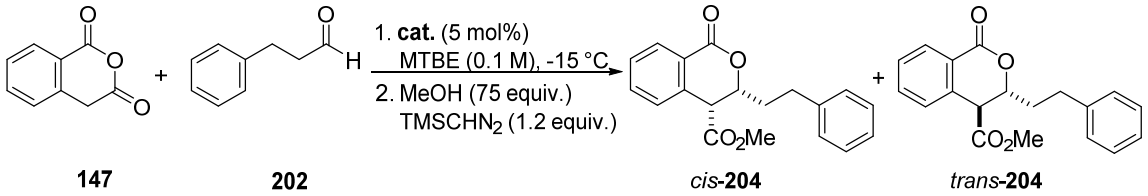


Figure 4.1 Structures of cinchona alkaloid-derived organocatalysts screened.

Table 4.1 Preliminary experiments involving the cycloaddition between homophthalic anhydride (**147**) and hydrocinnamaldehyde (**202**).



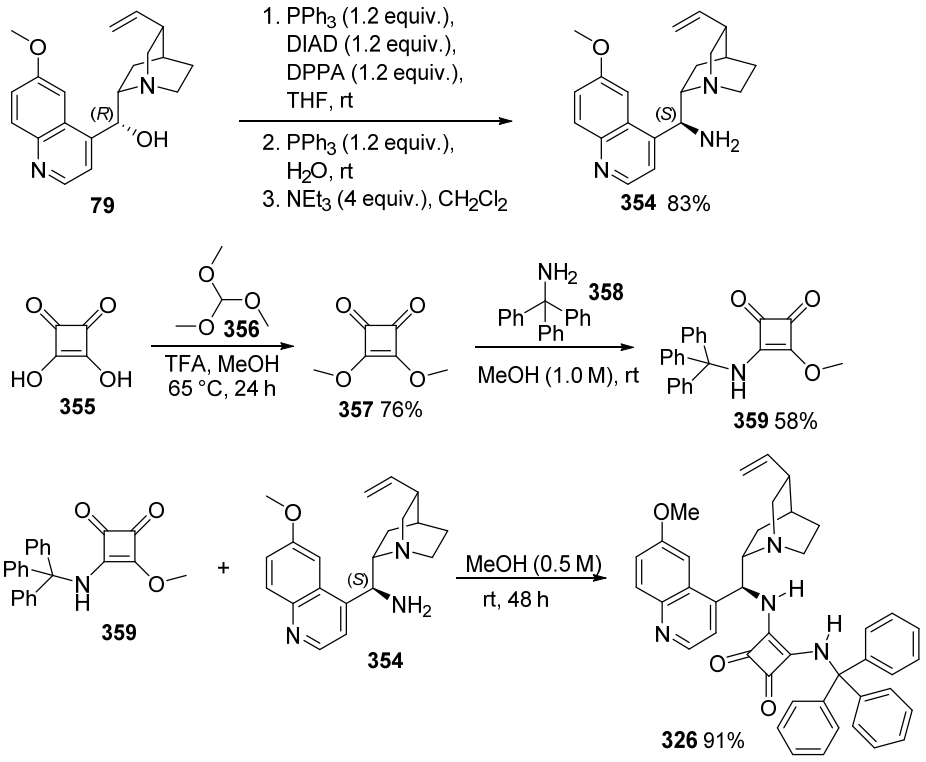
147 **202** *cis*-**204** *trans*-**204**

entry	catalyst	time (h)	yield (%)[a]	*dr* (*cis*:*trans*)[b]	*ee cis* (%)[c]	*ee trans* (%)[c]
1	**305**	120	79	46:54	0	20
2	**344**	48	99	40:60	87	98
3	**106**	120	91	40:60	rac	60
4	**345**	168	65	42:58	47	10
5	**346**	144	60	34:66	51	18
6	**304**	48	99	33:67	99	99
7	**200**	24	94	25:75	98	90
8	**347**	96	82	24:76	70	94
9	**348**	144	74	35:65	14	76
10	**349**	144	52	20:80	16	92
11	**350**	192	50	44:56	3	51
12	**351**	48	89	29:71	34	92
13	**352**	120	94	48:52	5	12
14	**353**	48	85	76:24	80	rac.
15	**326**	33	97	72:28	90	91

[a]Yield of combined diastereomers determined by ^{1}H NMR spectroscopic analysis using *p*-iodoanisole as an internal standard. [b]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis. [c]Determined by CSP-HPLC.

Introduction of a phenylglycine residue in its natural L- (**348**) and unnatural D-configuration (**349**) respectively, and a benzyl group (**347**) on the squaramide scaffold furnished the *trans*-diastereomer as the major product (entries 8-10), while the C_2-symmetric analogue **350** was found unsuitable for use in the reaction currently under

study (entry 11) due to unsatisfactory *dr* and *ee* of products yielded. We hypothesised that the exchange of an electron-deficient aryl group on the squaramide moiety in **304** or **200** for sterically hindered alkyl groups such as triethyl- or tricyclohexyl groups (**351** and **352**) could likely effect the catalytic performance, however this did not influence the *dr* of the transformation (entries 12 and 13). Surprisingly, in the presence of the trityl-substituted catalyst **326** and its substituted analogue **353** (synthesised by Mr. Romain Claveau) we were delighted to observe a complete reversal of the diastereoselectivity from 3:1 *trans*:*cis* for **204** to 3:1 *cis:trans* (entries 14 and 15). Both catalysts outperformed all of the other candidates, however catalyst **326** resulted superior to catalyst **353** as both diastereomers were afforded in remarkable enantiomeric excesses.



Scheme 4.2 Synthesis of catalyst **326**.

The synthesis of catalyst **326** was achieved by the four step procedure depicted in Scheme 4.2. It began with the Mitsunobu reaction of quinine (**79**) with triphenylphosphine (PPh_3), diisopropyl azodicarboxylate (DIAD) and diphenylphosphoryl azide (DPPA) - which allows for inversion of configuration at C-9' and substitution of the free alcohol functionality with an azide group. This was then reduced *in situ* to the free amino group by reaction with PPh_3 / H_2O to give product **354** in 83% yield.

Simultaneously, squaric acid (**355**) was converted to the corresponding dimethyl ester **357** by reaction with trimethyl orthoformate (**356**) and trifluoroacetic acid (TFA) in methanol at reflux. After isolation and purification by column chromatography, **357** was treated with trityl amine (**358**) in methanol at room temperature, affording **359** in 58% yield after filtration. The substrate **359** was reacted with **354** to furnish catalyst **326** in 91% yield (Scheme 4.2).

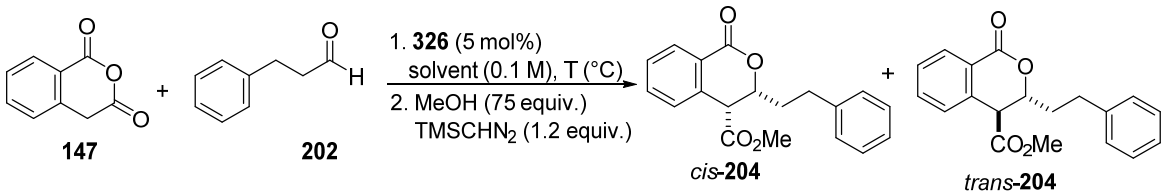
4.1.1 Further optimisation of reaction conditions

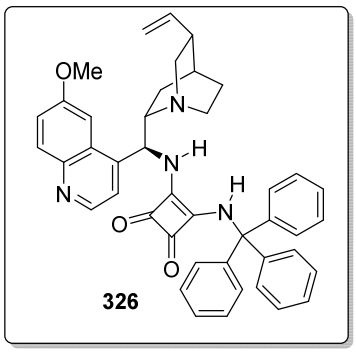
Prompted by the discovery that the trityl squaramide catalyst **326** provided high *cis*-diastereocontrol, we decided to move forward by optimising the reaction conditions. The influence of solvent and temperature were investigated in the formal cycloaddition reaction between homophthalic anhydride and hydrocinnamaldehyde using catalyst **326** - the results of this study are reported in Table 4.2.

Only ethereal solvents were examined here since previous studies within our group have shown them to increase the pK_a of the acid products formed, thus avoiding inhibition of the catalyst *via* protonation of quinuclidine moiety. The reaction performed in THF (entry 1) formed the *cis* product in high yield and *ee*, however no improvement in *dr* was observed (entry 1). A mixture of MTBE and THF gave comparable results with a slight increase in enantiomeric excess of the minor product (entry 2). 1,4-Dioxane, 2-methyltetrahydrofuran and 1,2-dimethoxyethane (entries 3-5) all exhibited similar profiles, furnishing the *cis*-product in remarkable yields but moderate *dr* of the major product. Lastly, the use of diisopropyl ether gave excellent enantioselectivity, however yield and *dr* were unsatisfactory (entry 6). From this screen, THF was shown to offer the best results from a diastereocontrol standpoint, so we kept with this solvent for further investigations.

We next examined the effect of temperature on catalytic performance. When the reaction was repeated at room temperature, decreased yields and stereocontrol were observed for both products (entry 7). Increasing the reaction temperature to 40 °C reduced the diastereocontrol (entry 8), while lowering the reaction temperature to -65 °C furnished better diastereo- and enantioselectivity, albeit in lower yield and with a longer reaction time (entry 9). Based on these results, -15 °C was considered the optimal temperature.

Table 4.2 Effect of solvent and temperature on the catalytic performance of **326**





entry	solvent	T (°C)	time (h)	yield (%)[a]	*dr* (*cis*:*trans*)[b]	ee_{cis} (%)[c]	ee_{trans} (%)[c]
1	THF	-15	48	99	71:29	99	91
2	MTBE/THF	-15	48	99	71:29	99	93
3	1,4-dioxane	rt	24	99	71:29	93	92
4	2-MeTHF	-15	24	99	71:29	95	93
5	1,2-dimethoxyethane	-15	48	99	71:29	99	94
6	diisopropyl ether	-15	144	62	63:37	99	89
7	MTBE	rt	48	80	71:29	95	88
8	THF	40	48	99	68:32	95	90
9	THF	-65	144	85	77:23	99	92

[a]Yield of combined diastereomers determined by ^{1}H NMR spectroscopic analysis using *p*-iodoanisole as an internal standard. [b]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis. [c]Determined by CSP-HPLC.

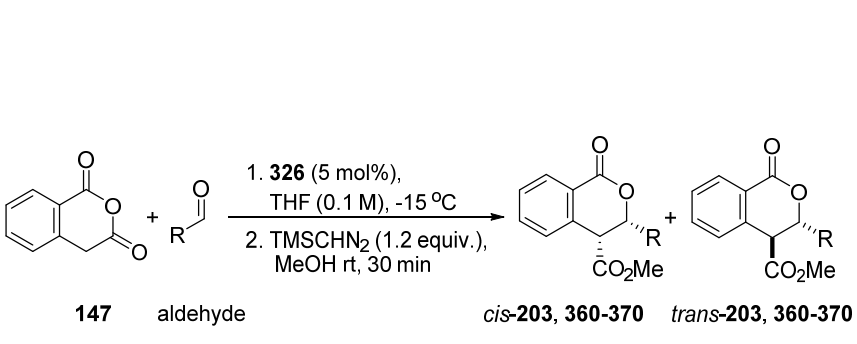
4.2 Evaluation of substrate scope: aliphathic aldehydes

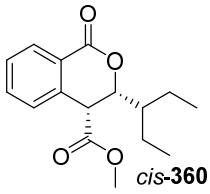
With optimised conditions in hand, we went about investigating the ability of catalyst **326** to promote the formation of the *cis*- over the *trans*-diastereomer in the reaction between various aliphatic aldehydes and homopthalic anhydride (Table 4.3).

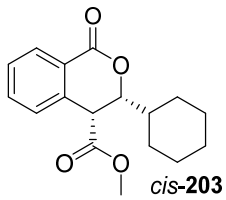
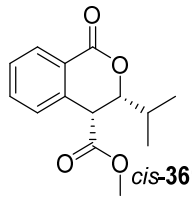
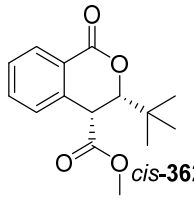
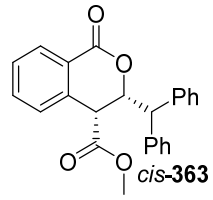
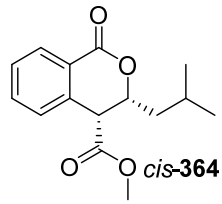
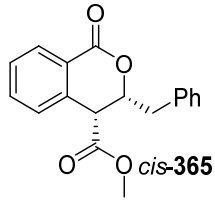
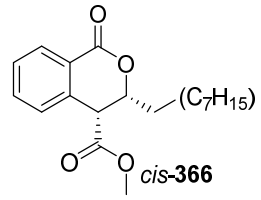
This methodology proved itself extremely robust when α-branched, straight chain, unsaturated aldehydes reacted with high levels of *cis*-diastereomer formation. When α-

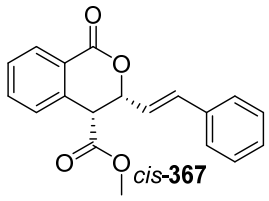
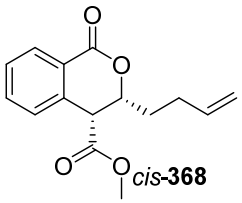
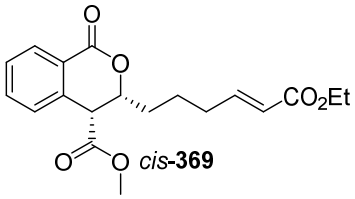
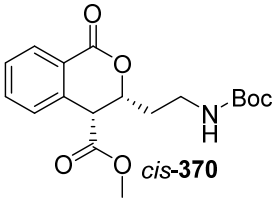
branched aldehydes were employed, **360**, **203**, and **361** were formed in a *dr* of approximately 4:1 to 9:1 - highlighting the significance of the substitution at the *α*-position to the carbonyl group (entries 1-3). However, trimethylacetaldehyde failed to react - probably due to significant steric hindrance (**362**, entry 4). Aromatic *α*-branched diphenylacetaldehyde was also tested, giving **363** in 87:13 *dr* and high optical purity (entry 5). Interestingly, the length of the straight chain aldehyde was shown to effect the diastereo- and enantiocontrol of the process, as isovaleraldehyde and phenylacetaldehyde, possessing shorter alkyl- and phenyl- substituted straight chains respectively (entries 6-7), furnished **364** and **365** in higher *dr* and *ee* compared to hydrocinnamaldehyde (**202**, Table 4.2, entry 1). The use of octanal led to good *cis*-diastereoselectivity, however a low *ee* of *trans* product (**366**, entry 8) was obtained. Unsaturated aldehydes were also well tolerated (entries 9-10), generally proceeding quickly with great yield and excellent enantioselectivity being observed for both diastereomers (**367** and **368** up to 84-98% *ee*). This methodology also allowed for a highly stereoselective preparation of synthetically malleable 3,4-dihydroisocoumarins **369** and **370** (entries 11-12).

Table 4.3 Evaluation of substrate scope: the aldehyde component.



entry	product	time (h)	yield (%)[a]	*dr* (*cis:trans*)[b]	ee_{cis} (%)[c]	ee_{trans} (%)[c]
1	 *cis*-**360**	144	90	90:10	99	99

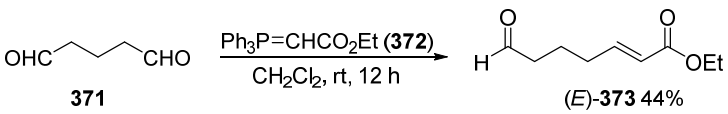
2	 *cis*-**203**	24	95	80:20	98	98
3	 *cis*-**361**	18	90	84:16	99	99
4	 *cis*-**362**	-	-	-	-	-
5	 *cis*-**363**	48	85	87:13	99	-
6	 *cis*-**364**	18	91	78:22	99	91
7	 *cis*-**365**	48	92	84:16	99	99
8	 *cis*-**366**	18	94	79:21	95	47

9	 *cis*-**367**	18	76	66:34	92	84
10	 *cis*-**368**	18	96	74:26	97	90
11	 *cis*-**369**	18	84	73:27	98	98
12	 *cis*-**370**	24	75	84:16	99	81

[a]Diastereomers not separable: combined isolated yield. after column chromatography. [b]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis. [c]Determined by CSP-HPLC.

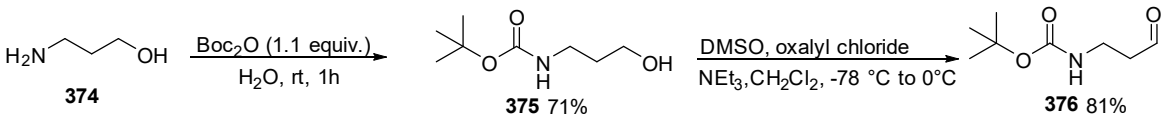
The aldehydes employed for the synthesis of dihydroisocoumarins **369** and **370** were prepared according to the procedure reported.

The substrate **373** was synthesised by the reaction between glutaraldehyde (**371**) and (carboethoxymethylene) triphenylphosphorane (**372**), furnishing the aldehyde **373** in 44% (Scheme 4.3).[217]



Scheme 4.3 Synthesis of aldehyde **373**.

The synthesis of aldehyde **376** was accomplished in two steps: Boc-protection of the 3-aminopropan-1-ol (**374**) to **375**, which then underwent a Swern oxidation in the presence of DMSO, oxalyl chloride and triethylamine to afford the desired product **376** in good yield (Scheme 4.4).[218, 219]



Scheme 4.4 Synthesis of aldehyde **376.**

The relative stereochemistry of **364** was found to be 3',4'-*cis*-**364**, as a coupling constant value of 3.3 Hz was measured between protons at positions C-4' and C-3'. With regards to the minor diastereomer, a coupling constant of 6.1 Hz was measured between the same protons in its ^{1}H NMR spectrum, allowing the assignment of its relative stereochemistry as 3',4'-*trans*-**364**.

In all the cases reported above, the *cis*-diastereomer could not be chromatographically separated from the *trans*-diastereomer, however isolation of *cis*-diastereomer was possible (albeit in low yield) by treating the mixture with isopropanol - in which the major product was found to be poorly soluble. Subsequent recrystallisation of the *cis*-diastereomer allowed for X-ray diffraction analysis in order to assign the absolute stereochemistry of the product *cis*-**364**. The result obtained led to the unequivocal assignment of the absolute stereochemistry of *cis*-**364** (Figure 4.2) as (3*R*,4*R*). This configuration was consequently assigned by analogy to all of the major diastereomers obtained *via* this methodology.

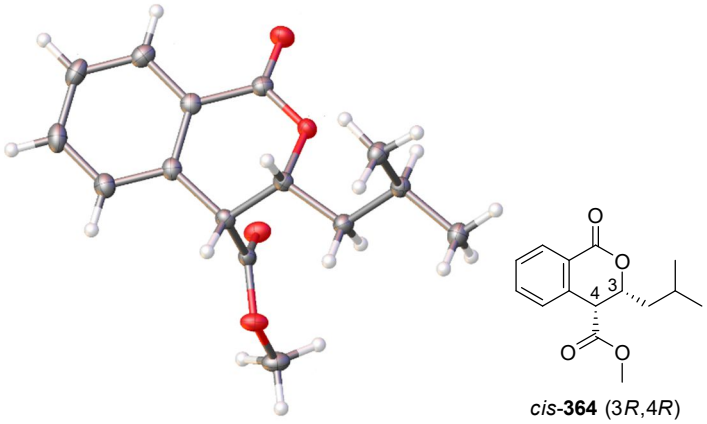
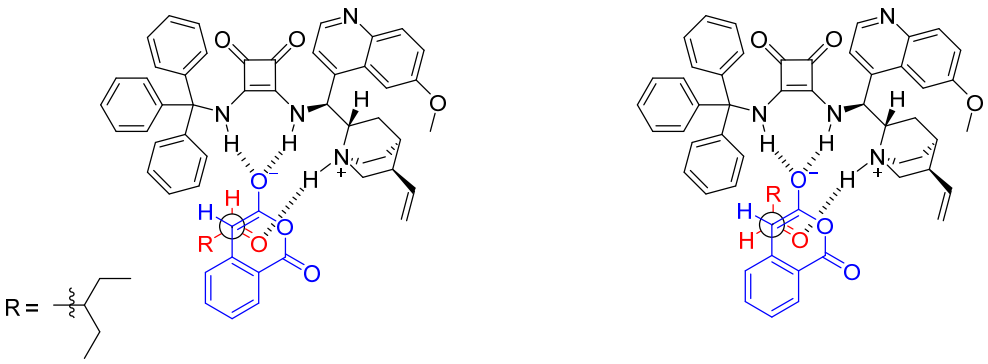


Figure 4.2 Absolute stereochemical assignment of product (3*R*,4*R*)-**364**.

4.2.1 Stereochemical outcome: rationale

In order to rationalise the stereochemical outcome of this process, Dr Trujillo carried out DFT (density functional theory) studies on the reaction between homophthalic anhydride **147** and 2-ethylbutyraldehyde (entry 1, Table 4.3). By analogy with observations made in the catalytic cycloaddition reaction between homophthalic anhydride and benzaldehyde (see Section 1.5.1.1),[159] we assumed that the reaction proceeds *via* 'specific-like catalysis'. The enolate, generated from deprotonation by the quinuclidine moiety, interacts with the squaramide moiety *via* a double hydrogen bonding interaction, while the aldehyde is activated by the protonated quinuclidine unit.

Our experimental data indicated that the two major stereoisomers yielded were (*R,S*)-**360** and (*R,R*)-**360**. Thus, based on the binding mode previously mentioned, we proposed two different pre-TS assemblies for both diastereomers (Figure 4.3) and studied their relative energy profiles (Figure 4.4). An overall analysis showed (computationally) that the pathway leading to (*R,S*)-**360** is favoured as the barriers associated with the formation of (*R,R*)-**360** are higher than those related to the formation of the more stable (*R,S*)-**360** (Figure 4.4). It is noteworthy that when starting at the catalyst-bound adduct, the barrier to its collapse to starting materials is lower than the barrier to lactonisation.



Binding mode A leading to (*R,S*)-**360** Binding mode A leading to (*R,R*)-**360**

Figure 4.3 Pre-TS assemblies leading to (*R,S*)-**360** and (*R,R*)-**360** according to binding mode A.

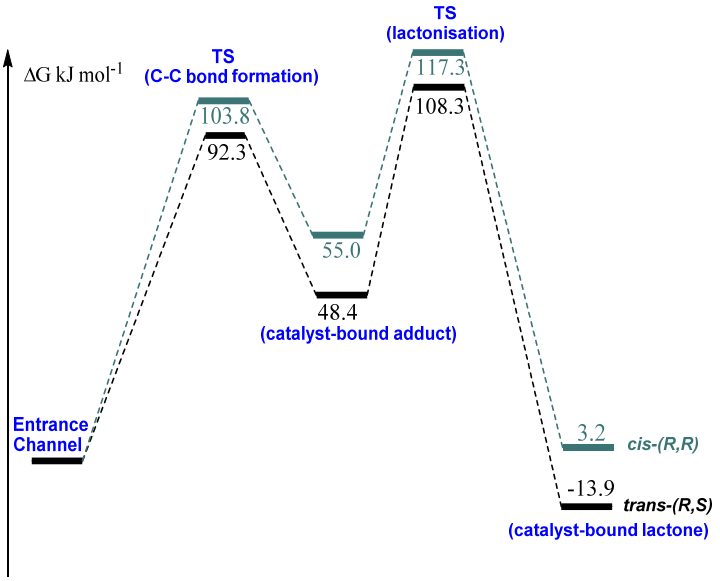
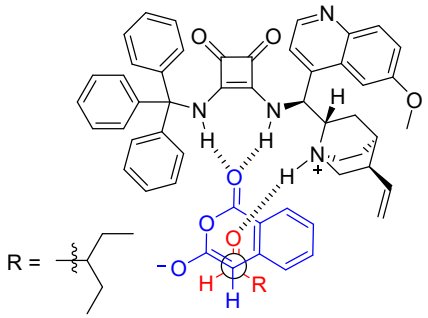
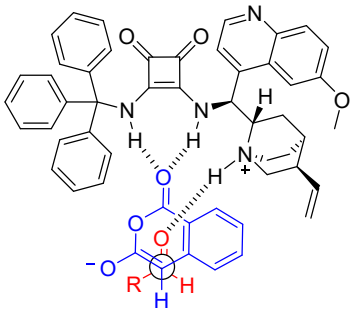


Figure 4.4 Potential energy surfaces for (*R,S*)-**360** and (*R,R*)-**360** complexes formed *via* binding mode A.

As this model was unable to explain the stereoinduction observed experimentally we investigated a second possible binding mode (B), in which two oxygen atoms of **147** are orientated towards the trityl group of **326** (Figure 4.5). In this case, higher energetic barriers were observed to the formation of the 1,2-adducts. However, the significantly lower energy of the *cis*-adduct (40.4 kJ mol^{-1}) relative to that of the *trans*-adduct (*R,S*) (76.3 kJ mol^{-1}), in addition to very similar barriers to its subsequent lactonisation or reversion to starting materials and a more stable *cis*-product, could potentially explain the origins of the observed sense of stereoinduction (Figure 4.6).



Binding mode B leading to (*R,S*)-**360**



Binding mode B leading to (*R,R*)-**360**

Figure 4.5 Pre-TS assemblies leading to (*R,S*)-**360** and (*R,R*)-**360** according to binding mode B.

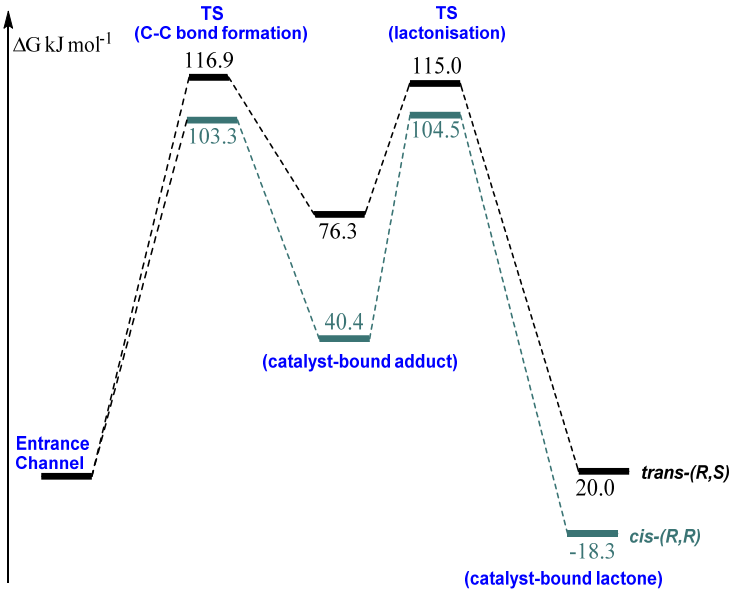


Figure 4.6 Potential energy surfaces for (*R,S*)-**360** and (*R,R*)-**360** complexes formed *via* binding mode B.

In further support of this hyphothesis, QTAIM (quantum theory of atoms in molecules) revealed that the stereochemical outcome is also governed by a web of attractive interactions involving hydrogen atoms on the trityl phenyl rings of **326** and the two oxygen atoms of **147**, which influence the facial selectivity of the attack of the anhydride enolate to the aldehyde (Figure 4.7). This also provides an explanation for the profound influence of the trityl unit on diastereocontrol, which is not mimicked by any other squaramide substituent evaluated.

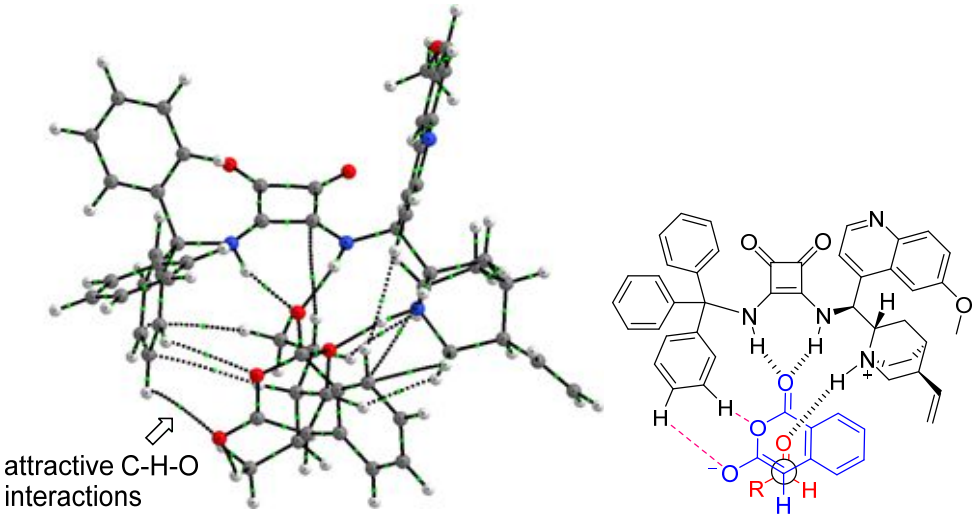
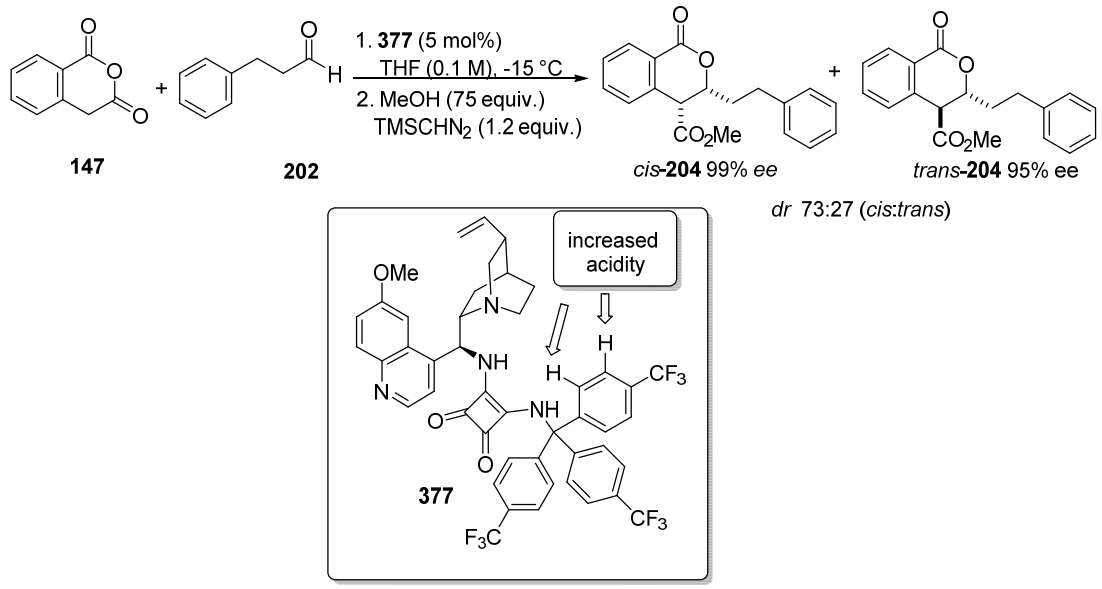


Figure 4.7 QTAIM interactions contributing to the formation of (*R,R*)-**360**.

The influence of these type of interactions on the stereocontrol of the reaction was demonstrated by evaluating the influence of electron-withdrawing and -donating functionality on the trityl moiety of **326**. The reaction reported in Scheme 4.5 was repeated under the optimised conditions in presence of catalyst **377** (synthesised by Mr Romain Claveau), which provided good *cis*-diastereo- and excellent enantioselectivity (Scheme 4.5). This result affirms the existence of these interactions in that the presence of -CF_3 in the *para* positions would increase the acidity of its adjacent protons, resulting in stronger interactions with the anhydride enolate. On the other hand, catalyst **353** (Table 4.1, entry 14), bearing -CH_3 in the *para* positions of the trityl phenyl rings, showed good diastereocontrol but inadequate enantioselectivity - likely due to the reduced acidity of the aromatic protons on the trityl moiety, which would result in weaker interactions with the anhydride enolate.



Scheme 4.5 Experiments involving the cycloaddition between homophthalic anhydride (**147**) and hydrocinnamaldehyde (**202**) using catalyst **377**.

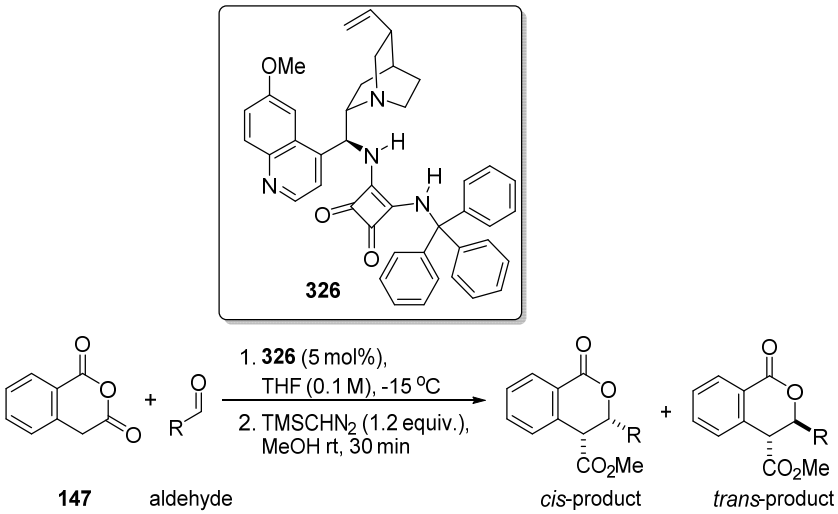
4.3 Evaluation of substrate scope: aromatic aldehydes

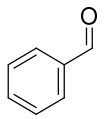
Until this point we had observed the *cis*-diastereoselectivity to be strongly dependent on two main factors: the steric and electronic properties of the trityl catalyst (**326**), and the aliphatic nature of the aldehyde. To probe the scope further, we turned our attention to the evaluation of aromatic aldehydes. We began this study by reacting benzaldehyde (**135**) with homophthalic anhydride (**147**) under the conditions presented in Table 4.4

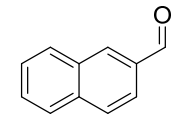
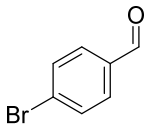
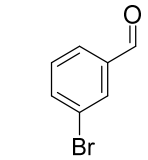
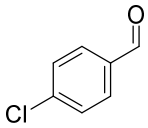
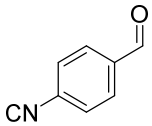
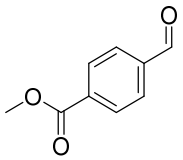
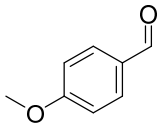
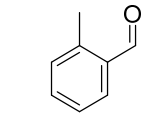
(entry 1). As expected, the use of trityl catalyst **326** reversed the *trans*-diastereoselectivity observed in studies mentioned in Section 1.5.1, however the exchange of an aliphatic for an aromatic aldehyde led to reduced diastereomeric ratios relative to those observed using aliphatic aldehydes - forming *cis*-**152** and *trans*-**152** in a ratio of 2:1. Entry 1 was also repeated at lower temperature (-70 °C) to see if any improvements in *dr* could be made, however only a slight improvement was observed (*dr* 66:34).

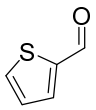
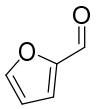
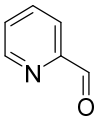
This methodology proved extremely robust, as hindered- (**378** entry 2) and electron-deficient/rich aldehydes (**379-383**, **157** and **49**, entries 3-9) were all well tolerated by the catalyst. Yields and enantiomeric excesses of both isolated diastereomers were generally good to excellent. Lactones **394**, **395**, and **396** derived from heterocyclic π-excessive aromatic aldehydes (*e.g.* **384**, **158**, and **385**, entries 10-12), were also found to be well compatible. Interestingly, furfural (**158**) underwent the most diastereoselective reaction in this screen-affording **395** in 74:26 *dr* but moderate *ee* (entry 10), which did not improve when lowering the temperature to -70 °C (*dr* 89:11, ee_{cis} 0%, *ee* 76%).

Table 4.4 Evaluation of substrate scope: the aldehyde component.



entry	aldehyde	prod.	time (h)	$yield_{cis}$ (%)[a]	$yield_{trans}$(%)[a]	*dr* (*cis:trans*)[b]	ee_{cis} (%)[c]	ee_{trans} (%)[c]
1	 **135**	**152**	120	54	35	61:39	94	64

2	 **378**	**386**	168	84[d]	84[d]	49:51	34	61
3	 **379**	**387**	22	54	36	60:40	94	74
4	 **380**	**388**	40	50	39	55:45	93	72
5	 **381**	**389**	36	54	37	59:41	95	78
6	 **382**	**390**	48	51	42	58:42	89	60
7	 **383**	**391**	48	55	38	59:41	88	83
8	 **157**	**392**	48	35	30	58:42	91	40
9	 **49**	**393**	96	58	28	67:33	95	82

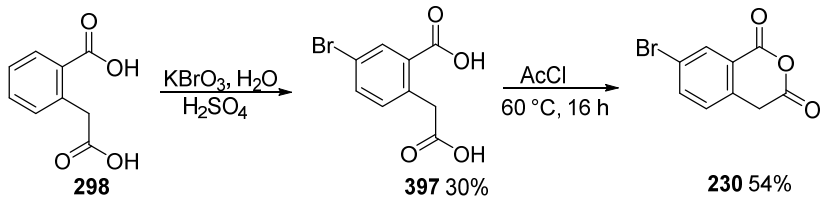
10	 **384**	**394**	144	50	37	56:44	88	57
11	 **158**	**395**	72	68	25	74:26	46	92
12	 **385**	**396**	96	58	32	61:39	84	25

[a]Isolated yield of the *cis*- and *trans*-diastereomers after column chromatography. [b]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis. [c]Determined by CSP-HPLC. [d]Diastereomers not separable: combined isolated yield after column chromatography.

4.4 Evaluation of substrate scope: substituted homophthalic anhydrides

After demonstrating the ability of the catalyst **326** to consistently favour the formation of the *cis*-diastereomer in the reaction with a range of aliphatic and aromatic aldehydes, we decided to examine its tolerance of different anhydrides - in particular substituted homophthalic anhydrides of disparate steric and electronic properties.

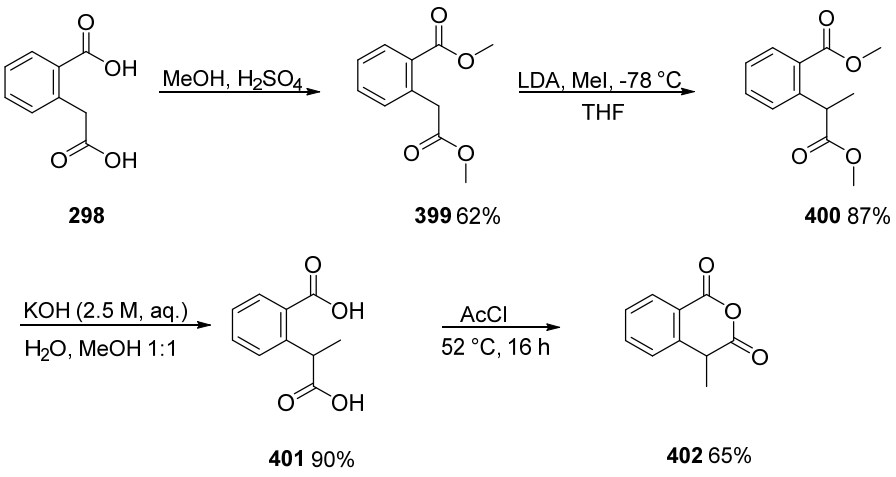
Methoxy-substituted anhydride **398** was kindly provided by Mr Aaròn Gutiérrez Collar, while the synthesis of the bromo-substituted homophthalic anhydride **230** was achieved following a procedure described by Balci *et al*.[220] (Scheme 4.6). Homophthalic acid (**298**) undergoes a regioselective bromination to furnish the dicarboxylic acid **397**, which was then converted to the corresponding bromo-substituted homophthalic anhydride **230** in moderate yield.



Scheme 4.6 Synthesis of bromo substituted homophthalic anhydride **230**.

Anhydride **402** was prepared according to another literature procedure[221] *via* the three step synthetic sequence depicted below. Fischer esterification of the dicarboxylic acid

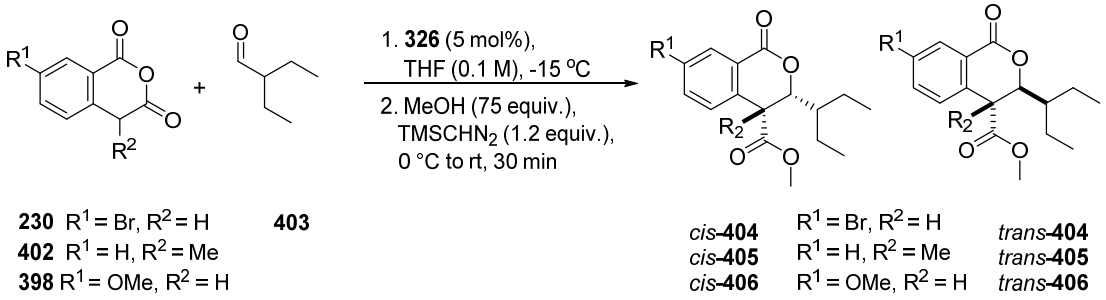
298 to **399** allowed α-methylation to **400**, which was subsequently hydrolysed to the corresponding acid **401** and closed to furnish the anhydride **402** in 65% yield (Scheme 4.7).



Scheme 4.7 Synthesis of methyl substituted homophthalic anhydride **402**.

We then began the examination of substituted homophthalic anhydrides **230**, **398** and **402** in reaction with 2-ethylbutyraldehyde (**403**) - selected as it previously gave excellent results in terms of *cis*-diastereo- and enantiocontrol (see Table 4.3, entry 1). Compound **404** was obtained in good yield, excellent *dr* and *ee* (entry 1). The use of C-5 substituted homophthalic anhydride **402** furnished *cis*-**405** and *trans*-**405** in a ratio of 1:1, with high *ee* being observed for the *cis*-product (entry 2). Meanwhile, as expected, incorporation of a deactivating methoxy group on homophthalic anhydride led to a sluggish reaction - forming of the *cis*-product (**406**, entry 3) in low enantiomeric excess.

Table 4.5 Evaluation of the substrate scope: homophthalic anhydride component.



entry	product	time (h)	yield (%)[a]	*dr* (*cis*:*trans*)[b]	ee_{cis} (%)[c]
1		216	71	84:16	99
2		96	43	54:46	97
3		240	67	80:20	57

[a]Isolated yield of the *cis*-diastereomer after column chromatography. [b]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis. [c]Determined by CSP-HPLC.

Only the *cis*-diastereomer was isolated after column chromatography, therefore all *ee* data refer to this diastereomer only. The relative stereochemistry of the products **404** and **406** were assigned by ^{1}H-NMR spectroscopic analysis of the crude reaction mixture by determination of the coupling constants between H-3 and H-4.

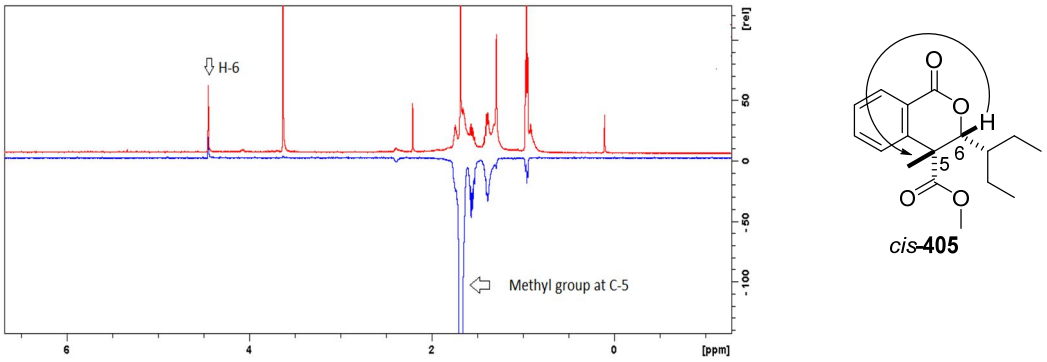
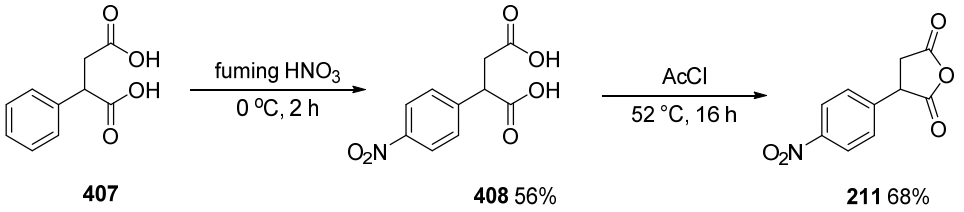


Figure 4.8 Assignment of the relative stereochemistry of **405** using a selective ROESY experiment.

However, the assignment of compound **405** required selective Rotating Overhause Effect (ROESY) experiments. Irradiation of the C-5 methyl group protons revealed an intense ROE correlation with H-6 (~4.5 ppm), showing that these groups interact through space - strongly suggesting a relative *cis* stereochemistry for **405** (Figure 4.8).

4.5 Evaluation of substrate scope: *p*-nitrophenyl succinic anhydride

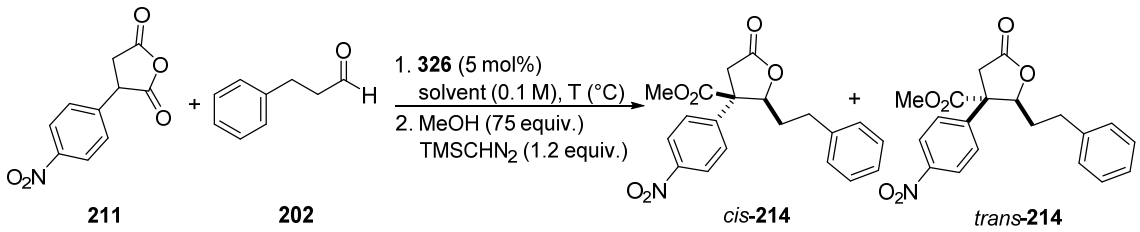
We next explored an extension of the scope to succinic anhydrides, in particular *p*-nitrophenyl succinic anhydride, and examined the possibility of achieving efficient *cis*-diastereocontrol in presence of trityl catalyst **326** and aliphatic aldehydes. The synthesis of 4-nitrophenyl succinic anhydride (**211**) was achieved by nitration of phenylsuccinic acid (**407**) to give **408**. The 4-nitrophenyl succinic acid (**408**) obtained was then converted to 4-nitrophenyl succinic anhydride (**211**) in 68% yield (Scheme 4.8).



Scheme 4.8 Synthesis of 4-nitrophenylsuccinic anhydride (**211**).

As depicted in Table 4.6, we first evaluated the anhydride **211** in the reaction with hydrocinnamaldehyde (**202**) under our optimised conditions (entry 1). We were pleased to observe that catalyst **326** reversed the *trans*-diastereoselectivity observed previously with squaramide catalyst **200**, from 72:28 for the *trans*-**214** to 90:10 in favour of *cis*-**214**, albeit in low *ee*. With the aim of improving the enantiocontrol, we attempted the same reaction in MTBE (entry 2), which increased the product *ee* to 61%, with a marginal decrease in *dr*. Lowering the temperature to -30 °C resulted in moderate enantioselectivity (entry 3), meanwhile at -75 °C, product **214** could be prepared in high enantiomeric excess without compromising the diastereocontrol (entry 4). Compared to homophthalic anhydride (**147**), the reactions involving *p*-nitrophenyl succinic anhydride (**211**) under identical reaction conditions proved to be significantly slower (comparing Tables 4.2 and 4.6), probably due to the requirement for the formation of a quaternary stereocentre using the latter anhydride. Overall, enantioselectivity was also lower using the succinic anhydride compared to the homophthalic analogue.

Table 4.6 Evaluation of *p*-nitrophenyl succinic anhydride as a substrate at different temperatures

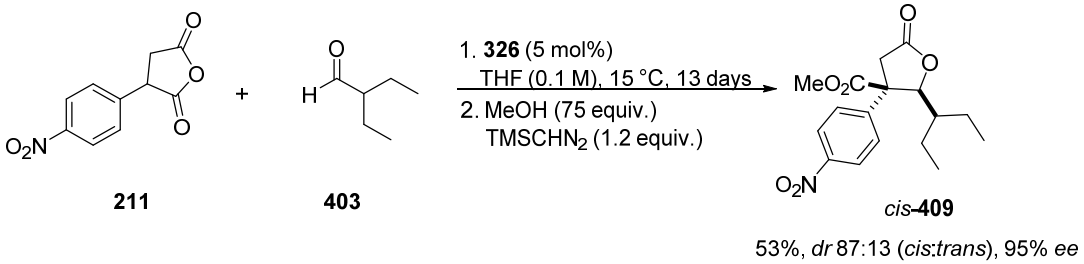


211 **202** *cis*-**214** *trans*-**214**

entry	time (h)	solvent	T (°C)	yield (%)[a]	*dr* (*cis:trans*)[b]	ee_{cis} (%)[c]
1	72	THF	-15	83	90:10	40
2	72	MTBE	-15	78	87:13	61
3	168	THF	-30	72	86:14	51
4	264	THF	-75	71	86:14	74

[a]Combined yield of the *cis*- and *trans*-diastereomers after column chromatography. [b]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis. [c]Determined by CSP-HPLC.

We also evaluated *p*-nitrophenyl succinic anhydride in the reaction with the 2-ethylbutyraldehyde (**403**) under the conditions reported in the Scheme 4.9. Product **409** was isolated as a major product in excellent optical purity (95% *ee*), but in low yield.



211 **403** *cis*-**409**

53%, *dr* 87:13 (*cis*:*trans*), 95% *ee*

Scheme 4.9 Reaction between *p*-nitrophenyl succinic anhydride and **403**.

The relative stereochemistry of compound **409** was assigned as depicted in Figure 4.9, again using ROE experiments. A ROE contact between the C-3 proton and H_a of the *p*-nitrophenyl moiety revealed these protons to be adjacent in space - allowing for the assignment of the relative stereochemistry of **409** as (2,3)-*cis*-**409**.

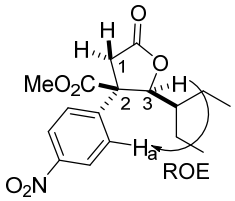
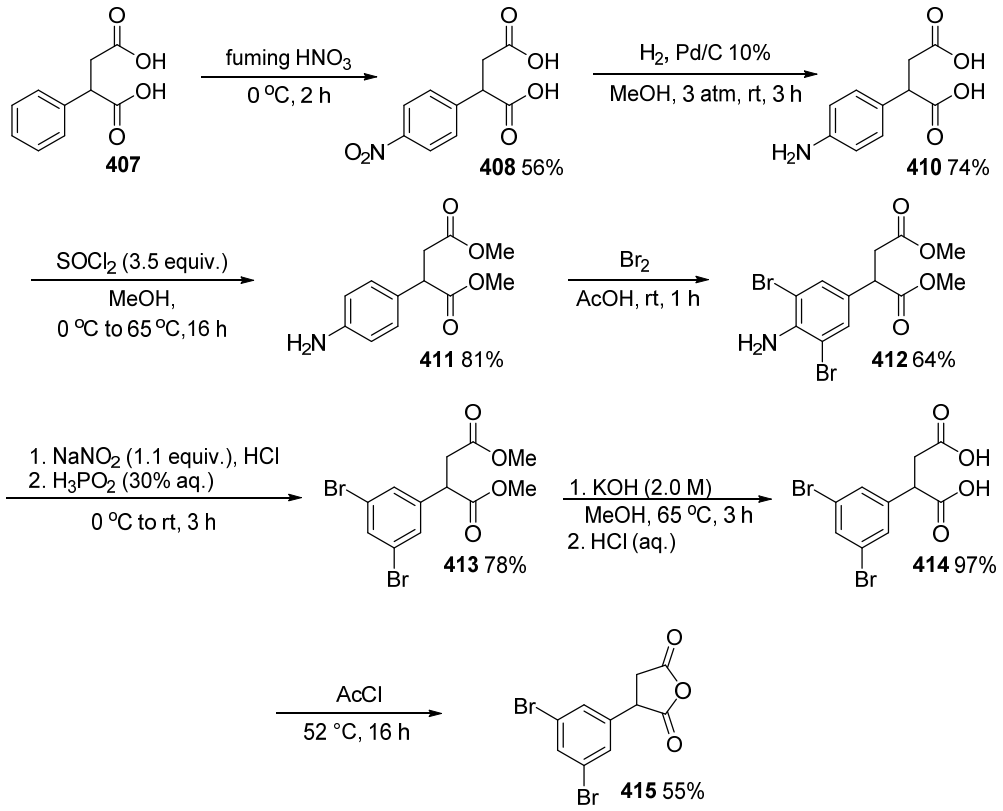


Figure 4.9 Relative stereochemistry of the diastereomer **409** determined by ROE NMR techniques.

4.6 Evaluation of substrate scope: substituted phenyl succinic anhydrides

Encouraged by the results reported in the previous Section, we decided to investigate the tolerance of this process for other phenyl succinic anhydride derivatives. We therefore went about the synthesis of different anhydrides bearing electron-withdrawing and -donating groups on the phenyl ring.

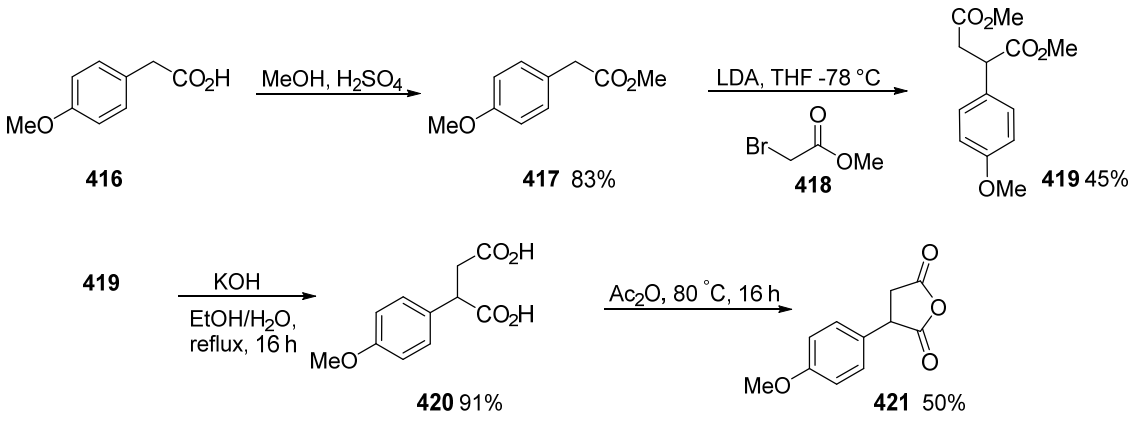


Scheme 4.10 Synthesis of 3,5-dibromophenylsuccinic anhydride **415**.

Anhydride **415** was first synthesised according to the procedure reported in the Scheme 4.10, starting with *para*-nitration of phenylsuccinic acid (**407** to **408**), followed by catalytic reduction of the nitro group to afford **410**, which was subsequently esterified to

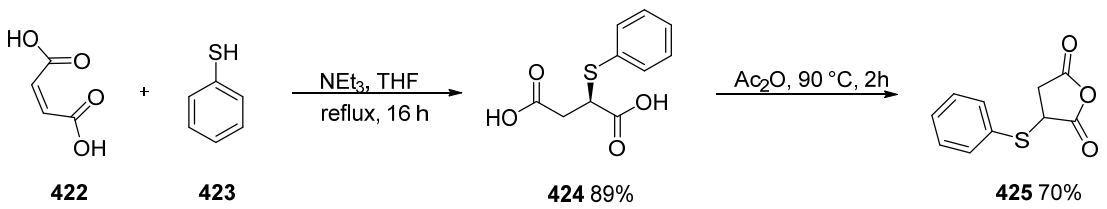
411, then di-brominated to furnish **412** in 64% yield. The amine **412** underwent diazotisation to the diazonium salt, which was reduced to the diester **413** in high yield. Subsequently hydrolysis furnished **414**, which was cyclised to the corresponding anhydride **415** in 55% yield (Scheme 4.10).

The anhydride **421** was synthesised in 17% overall yield in a four step synthetic sequence starting from the commercially available 4-methoxyphenylacetic acid **416** (Scheme 4.11). Fischer esterification of **416** gave **417** in 83% yield, which underwent alkylation with methyl bromoacetate (**418**) in the presence of LDA (prepared *in situ* at -78 °C). A subsequent basic hydrolysis of the esters in **419** furnished the corresponding diacid **420**, which was then transformed into 4-methoxyphenyl succinic anhydride **421** (Scheme 4.11).



Scheme 4.11 Synthesis of 4-methoxyphenyl succinic anhydride (**421**).

Anhydride **425** was synthesised in two steps starting by an initial conjugate addition of thiophenol (**423**) to maleic acid (**422**, Scheme 4.12). Compound **424** was subsequently cyclised with acetic anhydride to afford **425** in 70% yield.

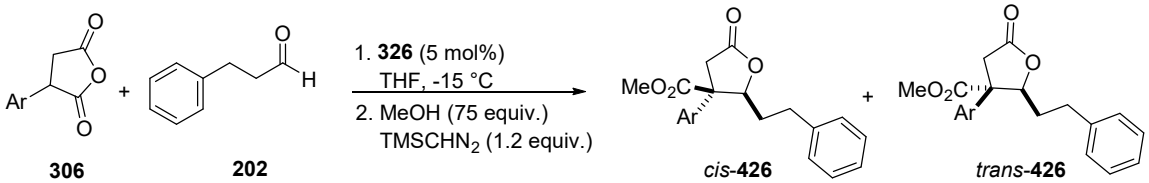


Scheme 4.12 Synthesis of thiophenyl succinic anhydride **425**.

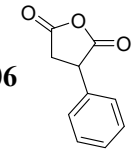
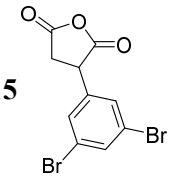
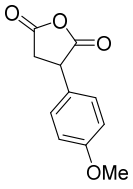
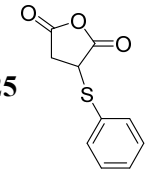
With these anhydrides in hand, phenyl succinic anhydride **306** (kindly provided by Ms Astrid Botte) was first evaluated under the conditions reported in Table 4.7, furnishing

the *cis*-diastereomer **426** in moderate yield and excellent enantiomeric excess (entry 1). Surprisingly, the reaction with 3,5-dibromo anhydride **415** favoured the formation of *trans*-**427** over *cis*-**427** – suspected to be due to the size of the anhydride, which probably influences binding within the transition state.

Table 4.7 Evaluation of phenyl succinic anhydride derivatives.



306, **415**, **421**, **425** + **202** → *cis*-**426**, *cis*-**427**, *cis*-**428**, *cis*-**429** + *trans*-**426**, *trans*-**427**, *trans*-**428**, *trans*-**429**

entry	substrate	prod.	time (h)	yield (%)[a]	*dr* (*cis*:*trans*)[b]	ee_{cis} (%)[c]	ee_{trans}(%)[c]
1	**306** 	**426**	360	61	83:17	93	67
2	**415** 	**427**	192	90	8:92	-	92
3	**421** 	**428**	360	30	80:20	71	61
4	**425** 	**429**	-	-	-	-	-

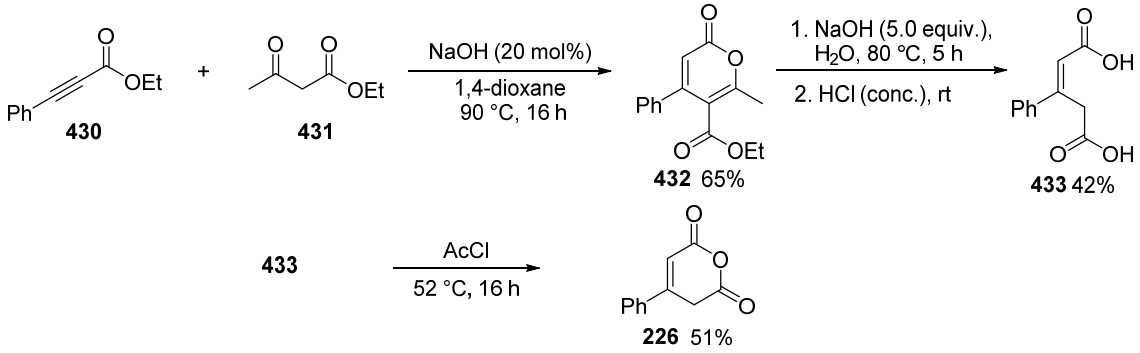
[a]Combined isolated yield of the *cis*- and *trans*-diastereomers after column chromatography. [b]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis. [c]Determined by CSP-HPLC.

Anhydride **421**, possessing an electron donating group (-OMe), required a noticeably longer reaction time to reach 30% conversion than the other anhydrides, but yielded

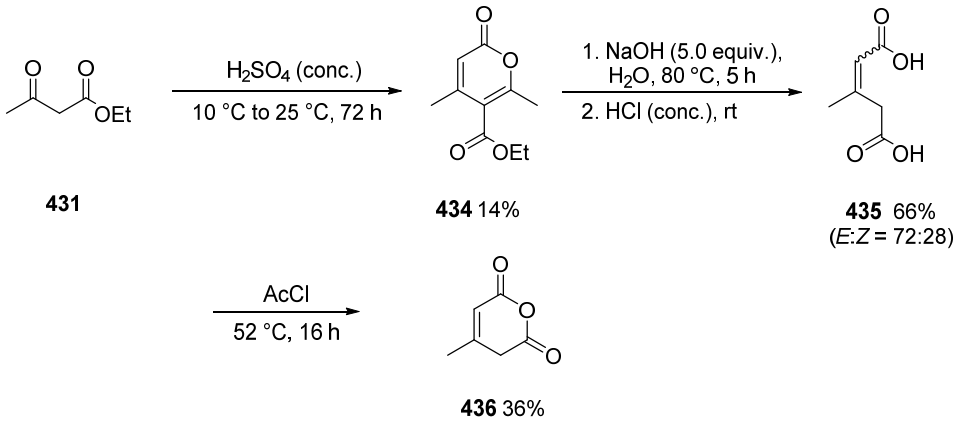
product **428** in good *dr* and *ee* (entry 3). Meanwhile, the reaction between anhydride **425** and hydrocinnamaldehyde did not take place (entry 4) - probably due to the low reactivity of the anhydride.

4.7 Synthesis of glutaconic anhydride derivatives

As reported previously (Section 1.5.3), 3,4-dihydropyrone represents a common framework in a number of kavalactone natural products. A retrosynthesis disconnection of this unit shows it may be synthesised by formal cycloadditions between anhydrides and aldehydes. Until now no cycloadditions between glutaconic anhydride derivatives and aldehydes have been reported in the literature. Thus, in order to study the feasibility of the process, a number of substituted glutaconic anhydrides were first synthesised - following known literature procedures reported below (Schemes 4.13, 4.14, 4.15).[177, 241, 242]



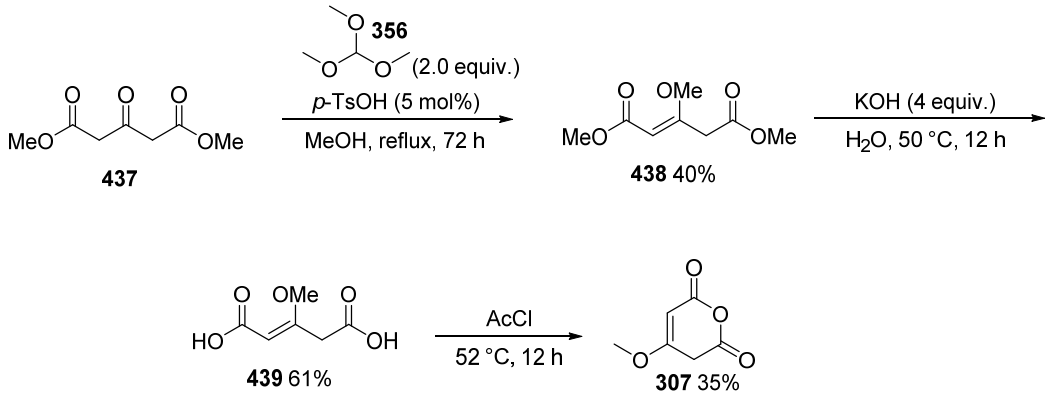
Scheme 4.13 Synthesis of anhydride **226**.



Scheme 4.14 Synthesis of anhydride **436**.

Substrates **226** and **436** were synthesised by cyclisation of their respective diacids (*e.g.* **433** and **435**) – obtained from hydrolysis of the lactone products **432** and **434**, formed from an intermolecular condensation process.

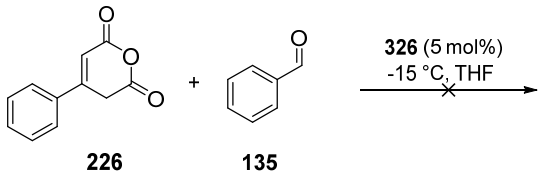
Anhydride **307** was produced from enol-etherification of **437** with trimethylorthoformate (**356**), followed by basic hydrolysis of the diester **438** and subsequent cyclisation of **439** using acetyl chloride.



Scheme 4.15 Synthesis of anhydride **307**.

4.7.1 Catalytic cycloaddition between glutaconic anhydrides and aromatic aldehydes

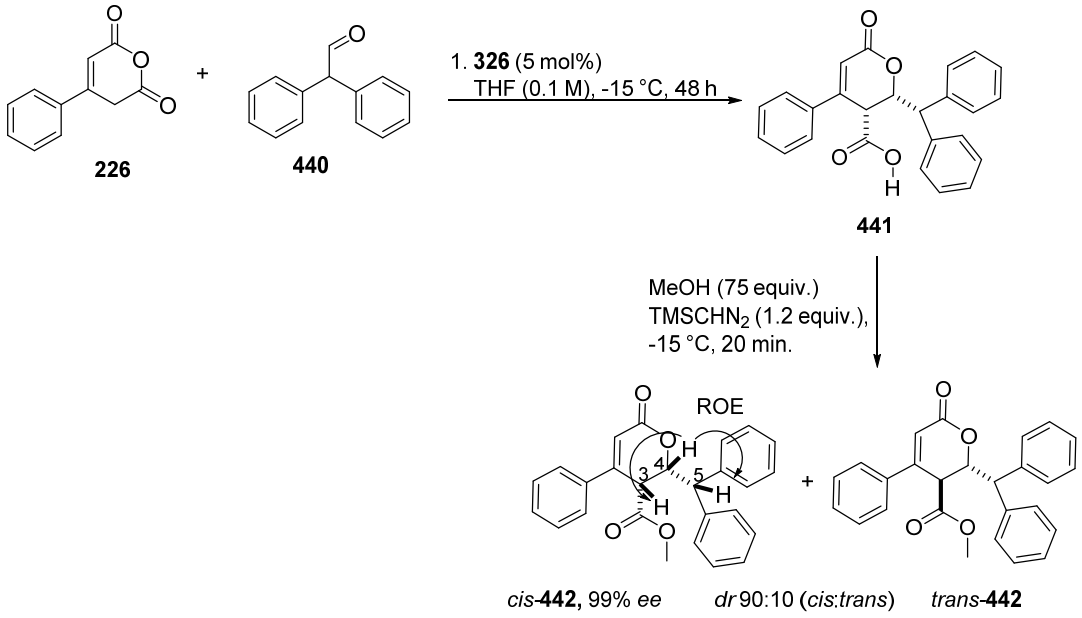
Our first attempt to effect a cycloaddition between a glutaconic anhydride and an aldehyde was with phenyl glutaconic anhydride **226** and benzaldehyde (**135**) in the presence of 5 mol% of catalyst **326** at -15 °C in THF (0.1 M). Disappointingly, the reaction failed to furnish the desired lactone; various unidentifiable side products were formed.



Scheme 4.16 Attempted cycloaddition between glutaconic anhydride and benzaldehyde promoted by catalyst **326**.

Moving forward, we decided to evaluate anhydride **226** with diphenylacetaldehyde (**440**) - an aldehyde previously reported to readily undergo cycloaddition with homophthalic

anhydride (see Table 4.3, Section 4.2). Under the conditions reported in Table 4.8 we found catalyst **326** was able to promote the cycloaddition - generating a single diastereomeric product (**441**). Lactone-acid **441** was then isolated *via* a base/acid extraction and analysed by ^{1}H NMR spectroscopy to assign its relative stereochemistry. The product was found to possess a *cis* conformation, as a coupling constant value of J = 1.4 Hz was measured between H-3 and H-4. This was further confirmed by ROE experiments, which revealed through-space interactions between protons H-3 and H-4, and between H-3 and H-5 respectively, allowing us to assume that these three protons are most likely on the same side of molecule.



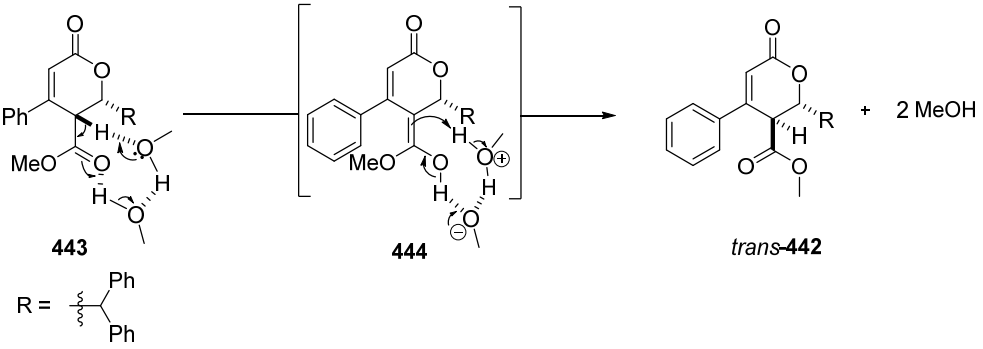
Scheme 4.17 Evaluation of phenyl glutaconic anhydride **226** and phenylacetaldehyde (**440**).

In order to determine the enantioselectivity of the process by CSP-HPLC, **441** was then converted to the corresponding lactone-ester **442** by reaction with $TMSCHN_2$ (1.2 equiv.) at -15 °C. After 20 minutes the crude mixture of esters was analysed by ^{1}H-NMR spectroscopy, which revealed the formation of a minor *trans*-diastereomer (based on the coupling constant between H-3 and H-4) – most likely due to an epimerisation process taking place which converted the *cis*-isomer to its *trans* counterpart. Despite this setback, the major product was isolated by chromatography and its enantiomeric excess quantified (99% *ee*, Scheme 4.17).

4.7.1.1 Optimisation of esterification procedure

At this stage we looked into the epimerisation issue which arose during the 'standard' esterification procedure using trimetylsilyldiazomethane ($TMSCHN_2$) and MeOH (75 equiv.), in case it should hinder our diastereocontrol moving forward.

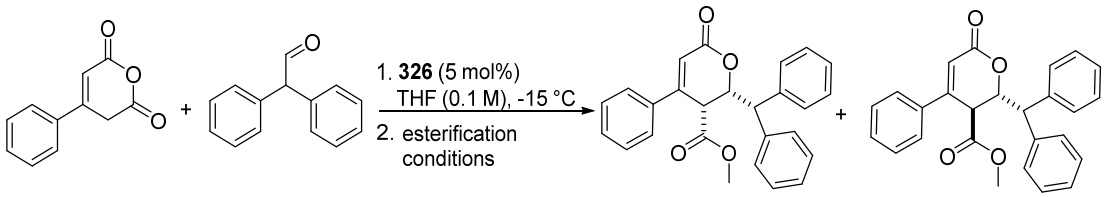
We postulated this process may be taking place *via* a similar mechanism to a computationally validated pathway which was proposed within our group (See Section 1.5.4).[178] By this mechanism, a hydrogen bonding complex involving two molecules of methanol (**443**) facilitates tautomerisation to the enol species **444**, which furnishes the corresponding *trans*-**442** after re-tautomerisation (Scheme 4.18).



Scheme 4.18 Proposed epimerisation mechanism.

Thus, we embarked on a series of experiments seeking to optimise the derivatisation procedure which could reduce epimerisation. Based on the proposed mechanism we thought that the use of more hindered alcohol in reasonable amounts could reduce the probability of that process occurring. To test this hypothesis we performed the reactions in EtOH (15 equiv.) at lowered temperature. After 20 minutes we analysed the reaction crude by ^{1}H-NMR spectroscopy and we observed 10% of the *trans*-isomer (entry 1). The *cis*-product was then isolated after column chromatography through silica gel and the enantiomeric excess estimated about 98% by CSP-HPLC. Identical result was obtained upon exchange of either ethanol or methanol with *i*PrOH (5 equiv.) at -15 °C (entry 2). Meanwhile esterification carried out in presence of MeI and DIPEA failed to afford the desired lactone-ester generating decomposed products instead. Finally the use of methyl triflate and triethylamine was also investigated. This protocol adopted could not fully suppressed the side reaction but did minimise it to 4%, keeping the product optical purity unchanged (entry 4) however in low yield.

Table 4.8 Epimerisation conditions.



226 **440** *cis*-**442** *trans*-**442**

entry	esterification condition	yield (%)[a]	*dr* (*cis*:*trans*)[b] (acids)	*dr* (*cis*:*trans*)[c] (esters)	ee_{cis} (%)[d]
1	EtOH (15 eq.), $TMSCHN_2$ (1.2 eq.), -30 °C	86	100:0	90:10	98
2	*i*PrOH (5 eq.), $TMSCHN_2$ (1.2 eq.), -15 °C	85	100:0	90:10	98
3	DIPEA (1.2 eq.), MeI (1 eq.), -15 °C	-	-	-	-
4	$CF_3SO_3CH_3$ (1 eq.), NEt_3 (1 eq.), -15 °C	62	100:0	96:4	98

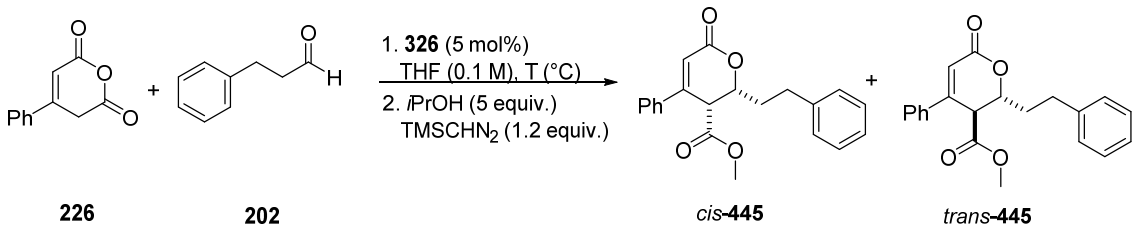
[a]Isolated yield of the *cis*-diastereomer after column chromatography. [b]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis before esterification. [c]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis after esterification. [d]Determined by CSP-HPLC.

4.7.2 Catalytic cycloaddition between glutaconic anhydride derivatives and aliphatic aldehydes

After achieving a good result in the evaluation of the aromatic α-branched aldehyde **440** we decided to investigate the applicability of this process to aliphatic aldehydes such as **202** and **403**.

We first reacted phenyl glutaconic anhydride **226** with hydrocinnamaldehyde (**202**) under our established optimal conditions (Table 4.9, entry 1). Contrary to what was described in the previous Section no variations in the *dr* of the products due to epimerisation upon esterification were observed using isopropanol and $TMSCHN_2$ at -15 °C. Good diastereocontrol was achieved, as *cis*-**445** was afforded in a ratio of almost 5 to 1 over the *trans*-**445** in a combined yield of 62%, albeit in low *ees*. In order to improve the enantioselectivities, we decreased the reaction temperature to -78 °C. Despite the higher *dr* obtained, both products were generated in poor enantiomeric excess. Therefore, we repeated the same reaction at room temperature, which surprisingly gave product **445** in higher enantio- and diastereoselectivity, showing a preference for *cis*-**445** (entry 3).

Table 4.9 Evaluation of phenyl glutaconic anhydride **226** and hydrocinnamaldehyde (**202**) at different temperatures



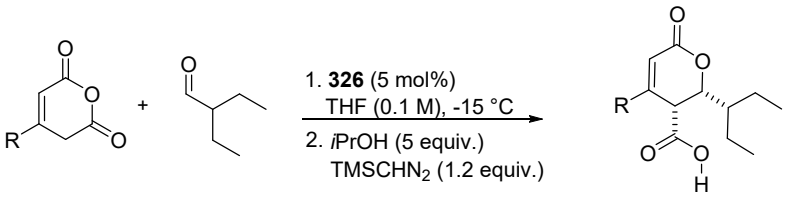
226 **202** *cis*-**445** *trans*-**445**

entry	time (h)	T (°C)	yield (%)[a]	*dr* (*cis*:*trans*)[b]	ee_{cis} (%)[c]	ee_{trans} (%)[c]
1	18	-15	63	82:18	7	10
2	240	-78	60	88:12	7	10
3	18	rt	64	86:14	76	45

[a]Combined isolated yield of the *cis*- and *trans*-diastereomers after column chromatography. [b]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis. [c]Determined by CSP-HPLC.

We next investigated various glutaconic anhydride derivatives in the reaction with the 2-ethylbutyraldehyde (**403**) under the conditions depicted in Table 4.10. Disappointingly, anhydrides **436**, **307** and **446** failed to form the corresponding products **448**-**450** (entries 2-4). Meanwhile, the reaction involving phenyl glutaconic anhydride produced one single diastereomer (*e.g.* **447**) in almost optical purity (entry 1).

Table 4.10 Evaluation of glutaconic anhydride derivatives and 2-ethylbutyraldehyde (**403**)



226 R = Ph
436 R = Me
307 R = OMe
446 R = Cl

403

447 R = Ph
448 R = Me
449 R = OMe
450 R = Cl

entry	substrate	product	time (h)	yield (%)[a]	*dr* (*cis*:*trans*)[b]	ee_{cis} (%)[c]
1	**226**	**447**	72	56	95:5	99
2	**436**	**448**	-	-	-	-
3	**307**	**449**	-	-	-	-

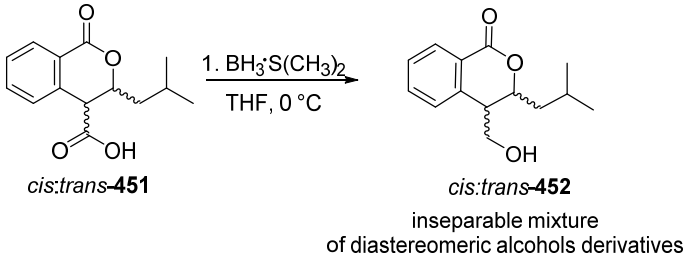
4	**446**	**450**	-	-	-	-

[a]Isolated yield of the *cis*-diastereomer after column chromatography. [b]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis. [c]Determined by CSP-HPLC.

4.8 Derivatisation protocol development

As mentioned previously this new methodology offered the possibility of synthesising *cis*-products in good yields and excellent optical purity. However, most of the compounds obtained were isolated as mixtures of the *cis*- and *trans*- diastereomers which were inseparable as they possess identical retention factors (Rf). Despite intensive efforts devoted to the separation of these diastereomers either as methyl ester derivatives or as carboxylic acids (isolated after work up) by column chromatography, no separation could be achieved. We also attempted separation using an automated flash chromatographic purification system (*e.g.* Biotage SP4), which employs high performance prepacked silica cartridges – to no avail.

At this stage we considered the possibility of derivatising the *cis*- and *trans*-acid lactones as alcohols or amides, hypothesising that the diastereomers formed would be easily separable by chromatography on silica gel. We first repeated the reaction reported in Table 4.3 (entry 6). After full conversion, the acid products **451** were isolated through an acid/basic work up, then dissolved in THF (2.0 M) and converted to the corresponding alcohol derivatives **452** by selective reduction of the carboxylic acid functionality in the presence of borane dimethyl sulphide complex.

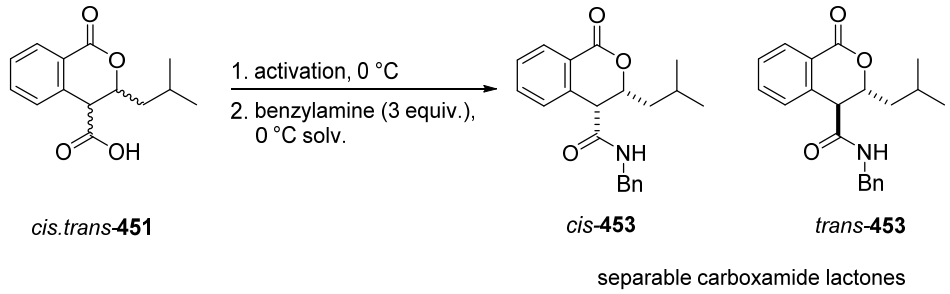


Scheme 4.19 Derivatisation of acids **451** as alcohols **452**.

Subsequent purification of the mixture on silica gel revealed the two alcohol derivatived lactones were not chromatographically separable (Scheme 4.19). Thus, we then decided to react the 3,4 dihydroisocoumarine-4-carboxylic acids (**451**) with benzylamine - all attempts of which are reported in the Table 4.11.

Performing the reaction in the presence of HBTU (2- (1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) and DIPEA led to formation of a mixture of unidentified side products (entry 1). Meanwhile, when the mixture of *cis*:*trans*-**451** (in a ratio 78:22) was reacted with benzylamine in the presence of DCC and DMAP at 0 °C - the corresponding mixture of *cis*- and *trans*-carboxamide lactones were formed in a ratio of 65:35 (entry 2). However, a difference in *dr* was detected by ^{1}H-NMR spectroscopic analysis before and after this reaction – suggesting an epimerisation process occurred. Unfortunately the same drawback was observed when carring out the reaction with EDC at 0 °C (entry 3).

Table 4.11 Derivatisation as amide



cis.trans-**451** *cis*-**453** *trans*-**453**

separable carboxamide lactones

entry	conditions	yield$_{cis}$ (%)[a]	yield$_{trans}$ (%)[b]	*dr* (*cis*:*trans*)[c]	*dr* (*cis*:*trans*)[d]
1	HBTU (1.1 equiv.), DIPEA (1.1 equiv.), CH_2Cl_2, 48 h	-	-	78:22	-
2	DCC (1.5 equiv.), DMAP (0.1 equiv.), CH_2Cl_2, 0 °C, 48 h	70	20	78:22	65:35
3	EDC (1 equiv.), CH_2Cl_2, 48 h	70	20	78:22	64:36
4	Oxalyl chloride (1 equiv.), DMF, 24 h	70	20	78:22	78:22

[a]Isolated yield of the *cis*-diastereomer after column chromatography. [b]Isolated yield of the *trans*-diastereomer after column chromatography. [c]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis before derivatisation. [d]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis after derivatisation.

Thus, we decided to adopt another strategy which employed one equivalent of oxalyl chloride and 2 drops of DMF at 0 °C for one hour – converting the carboxylic acid **451** to its acyl chloride (entry 4). This was then used in the next step without further purification and an excess of benzylamine (3 equivalents) was added to allow the

formation of the corresponding carboxamide **453** –leading to unchanged *dr* and enantiomeric excess. Subsequent purification by column chromatography allowed for the complete separation of the *cis*- and *trans*-**453** which were isolated as single diasteromers.

4.9 Conclusion

The results obtained in this project have demonstrated the possibility to reverse the *trans*-diastereoselectivity previously observed in organocatalytic asymmetric formal cycloaddition reactions between cyclic enolisable anhydrides and various aliphatic aldehydes by choice of a bulky substituted squaramide catalyst. This process has provided one-pot access to functionalised *cis*-lactone derivatives such as dihydroisocoumarins and γ-butyrolactones in good yield and high stereocontrol. Furthermore, we demonstrated for the first time the expansion of the scope of the anhydride component to phenyl glutaconic anhydride, allowing for the synthesis of 3,4-dihydropyrones – core units present in a range of natural products possessing interesting medicinal properties.

Computational studies have shed light on the stereochemical outcome observed, and the absolute configuration of the products obtained has been assigned by direct analogy and X-ray crystallography.

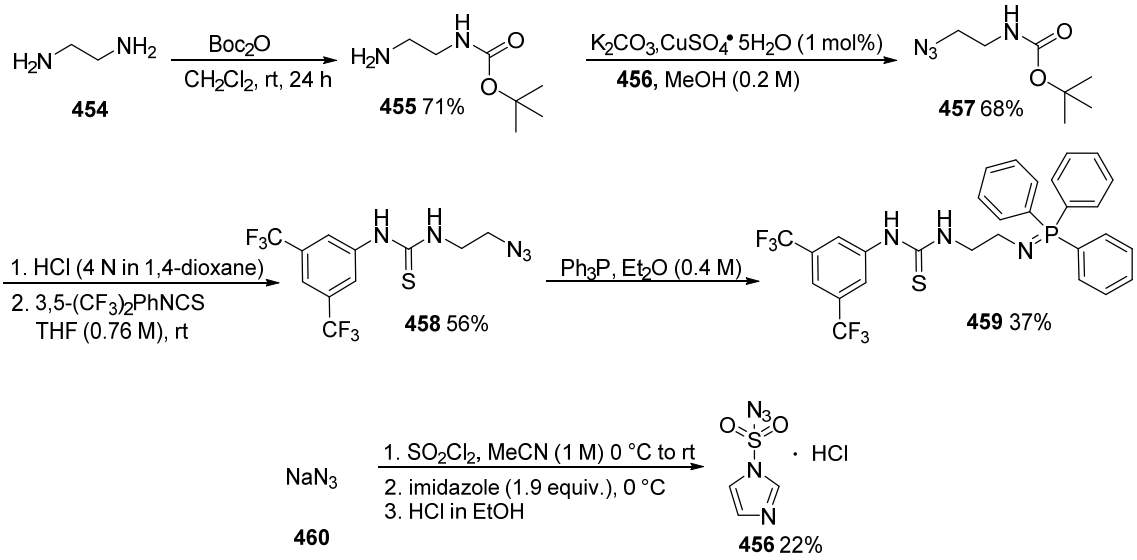
5. Use of bifunctional iminophosphazenes in the cycloaddition reaction between enolisable anhydrides and aldehydes

As mentioned in Sections 1.5.1 and 1.5.2, the rate-limiting step in cinchona alkaloid catalysed cycloaddition reactions between enolisable anhydrides and electrophiles is in part, the formation of the enolate species - promoted *via* deprotonation by the quinuclidine moiety. When aromatic anhydrides bearing an electron widrawing group were employed, the reaction proceeded at higher rates as a consequence of greater concentrations of enolate in solution. On the other hand, anhydrides lacking functionality which is able to stabilise the enol species react slowly, if at all.

A potential approach to overcome the low nucleophilicity of some anhydrides due to their poor enolisability is to enhance the Brønsted basicity of the catalyst itself. Thus, we turned our attention to a new class of catalysts: bifunctional iminophosphorane superbase catalysts. We believed that the strong Brønsted basicity of a triaryliminophosphorane unit could provide sufficient activation of weak pronucleophiles, while an incorporated H-bond donor group attached to a suitable chiral scaffold could activate the electrophilic component.

5.1 Synthesis of bifunctional iminophosphorane catalyst 459

Our studies began with the synthesis of the achiral bifunctional iminophosphorane catalyst **459**, which was formed in 10% overall yield by a five step synthetic procedure starting from the commercially available 1,2 ethylenediamine **454**. This underwent Boc-protection of one of the amino groups to provide **455**, which was then converted to the Boc-azide **457** in the presence of imidazole-1-sulfonyl azide hydrochloride (**456**) and catalytic amounts of $CuSO_4 \bullet 5H_2O$ (copper sulphate pentahydrate). Subsequent Boc-deprotection affords the corresponding aminoazide, which reacts with *bis*-3,5-(trifluoromethylphenyl)-isothiocyanate *in situ* to furnish the azidothiourea **458**. Finally, a Staudinger reaction afforded the catalyst **459** (Scheme 5.1).

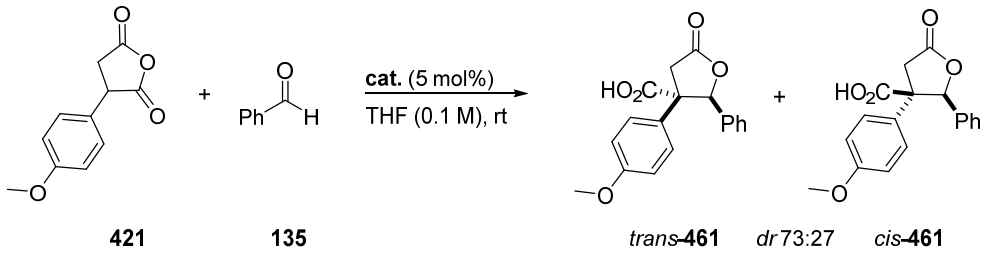


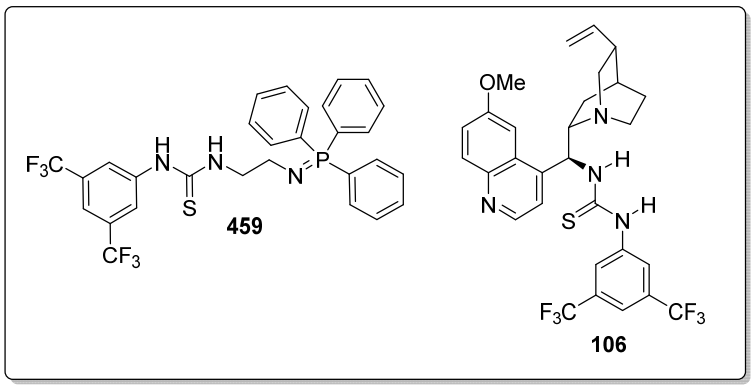
Scheme 5.1 Synthesis of catalyst **459** and imidazole-1-sulfonyl azide hydrochloride. **456**.

5.2 Preliminary studies: evaluation of substrate 421 and 425

With a bifunctional superbase organocatalyst in hand we first tested its catalytic ability in the formal cycloaddition reaction between *p*-methoxyphenyl succinic anhydride **421** and benzaldehyde **135** under the conditions depicted in Table 5.1. This reaction was attempted in the presence of squaramide cinchona alkaloid catalyst **200**, yielding only 7% of the product after 4 days.[168] The low yield observed was undoubtedly due to the presence of an electron donating group on the aryl unit which destabilises the formation of the enol. We hoped that the use of a superbase catalyst could improve the product conversion and the rate of reaction by increasing the concentration of the enol in solution. Thus, we conducted some kinetic studies, monitoring the conversion over time by ^{1}H-NMR spectroscopic analysis of the crude reaction mixture (Table 5.1). In order to obtain a direct comparison we carried out the same experiment with the thiourea based cinchona alkaloid catalyst **106** in parallel. In both cases no product was detected after 10 minutes (entry 1). The reaction with catalyst **459** proceeded only slightly faster (entries 2 and 3), showing no significant increase in conversion after 32 h - possibly due to degradation of catalyst (entry 4).

Table 5.1 Kinetic studies on the cycloaddition reaction between anhydride **421** and benzaldehyde (**135**).



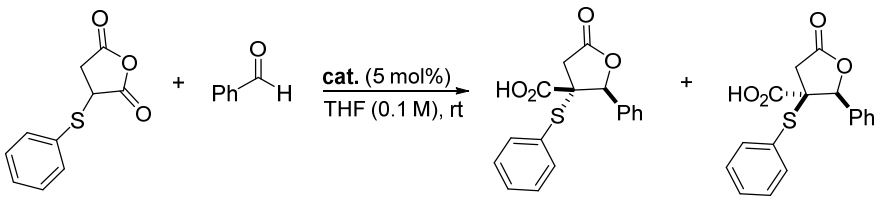


entry	time (h)	yield (%)[a] using cat. 459	yield (%)[a] using cat. 106
1	10 min	-	-
2	18	5	3
3	24	7	6
4	32	13	9

[a]Yield of combined diastereomers determined by ^{1}H NMR spectroscopic analysis using *p*-iodoanisole as an internal standard.

A ^{1}H-NMR spectroscopic kinetic experiment was also carried out for the reaction involving 2-thiophenyl succinic anhydride (**425**) and benzaldehyde (**135**). As reported in Section 4.6, **425** was found to be unreactive in the cycloaddition reaction with aliphathic aldehyde **202** promoted by trityl catalyst **326**. Consistent with what was observed previously, the superbase catalyst **459** outperformed **106**, giving more conversion over time (entries 1-4, Table 5.2).

Table 5.2 Kinetic studies in the cycloaddition reaction between anhydride **425** and benzaldehyde (**135**)



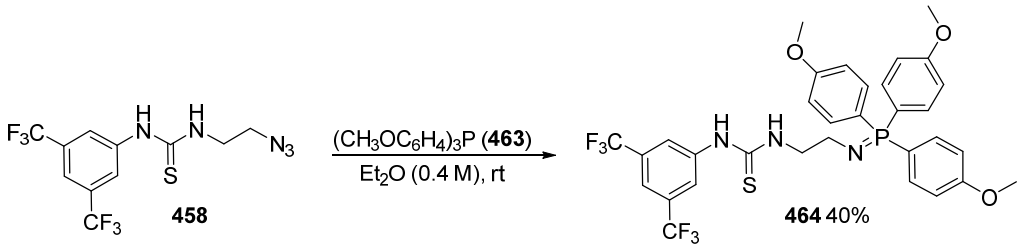
425 **135** *trans*-**462** *dr* 75:25 *cis*-**462**

entry	time (h)	yield (%)[a] using cat. 459	yield (%)[a] using cat 106
1	2	-	-
2	168	11	3
3	288	13	6
4	720	13	6

[a]Yield of combined diastereomers determined by ^{1}H NMR spectroscopic analysis using *p*-iodoanisole as an internal standard.

5.3 Catalyst design

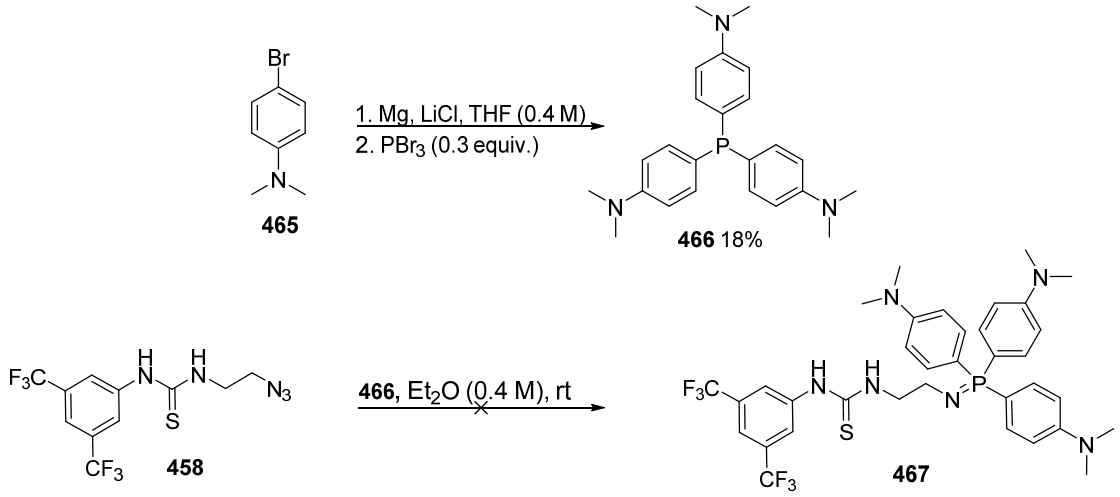
Although our preliminary results demonstrated that the higher basicity of catalyst **459** led to greater catalytic activity than **106**, the rate of reaction was still low, leading us to consider designing a more powerful bifunctional iminophosphorane catalyst possessing greater Brønsted basicity. Inspired by Dixon's studies (see Section 1.7.1), we decided to modify the triaryliminophosphorane moiety by varying the electronic properties of the triarylphosphine component. We believed that the incorporation of electron-donating groups such as methoxy (-OMe), or dimethyl amine groups (-N(CH$_3$)$_2$) on phenyl ring units would create a stronger iminophosphorane base capable of accelerating the rate of reaction.



458 **464** 40%

Scheme 5.2 Synthesis of catalyst **464**.

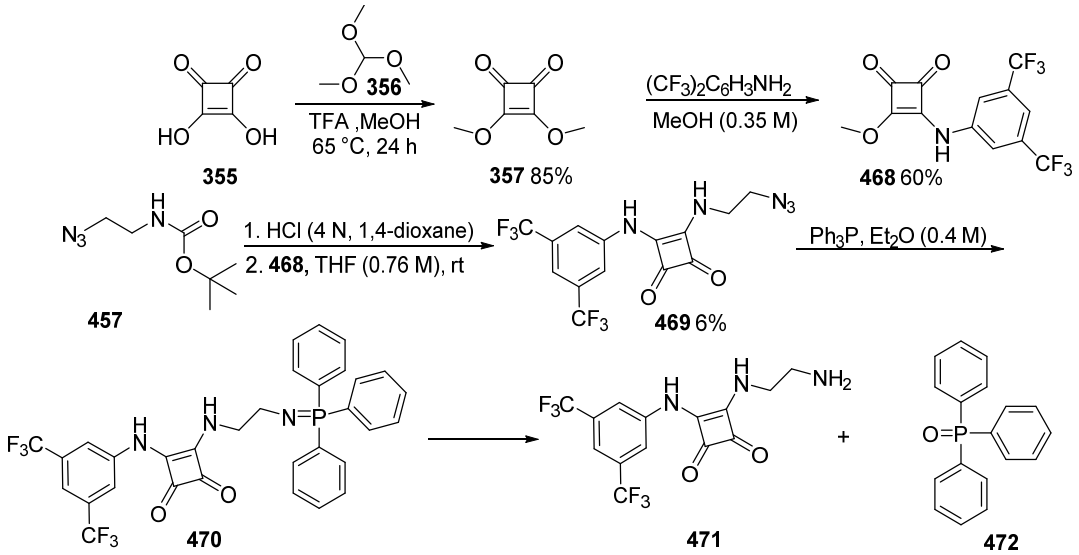
Catalyst **464** was prepared *via* Staudinger reaction between the thiourea azide **458** and the commercially available *tris*(4-methoxyphenyl)phosphine (**463**, Scheme 5.2). Using a similar strategy we also attempted the synthesis of catalyst **467**. The substituted triphenylphosphine **466** was prepared starting from 4-bromo-*N*,*N*-dimethylaniline (**465**). A subsequent Staudinger reaction between **458** and **466** failed to furnish the corresponding product, mainly due to its degradation *in situ* (Scheme 5.3).



Scheme 5.3 Attempted synthesis of **467**.

We later investigated modification of the H-bond moiety. The superiority of the squaramide unit as a H-bond donor in the activation of a range of electrophiles (see Section 1.2.3) led us to the design of novel catalyst **470**, the attempted synthesis of which was carried out following the procedure depicted in the Scheme 5.4 below.

The H-bond unit was first synthesised by converting squaric acid (**355**) to the dimethyl ester **357**, which was substituted with 3,5-*bis*(trifluoromethyl)-aniline to furnish **468**. Compound **457** was then reacted with **468** upon deprotection to give **469** in just 6% yield, which subsequently underwent a Staudinger reaction with triphenylphosphine at room temperature. Disappointingly, **470** could not be isolated due to its degradation in solution *via* hydrolysis - forming triphenylphosphine oxide (**472**) and the corresponding amine **471**, both of which were observed by ^{1}H-NMR spectroscopic analysis of the crude, and also detected by APCI mass spectrometry.



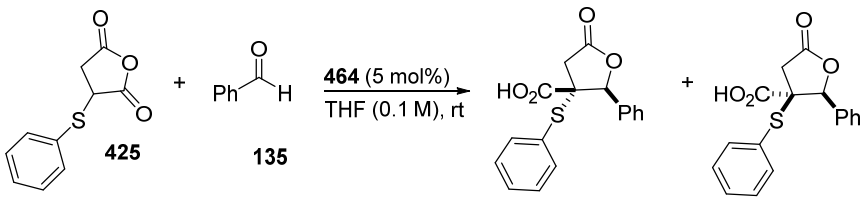
Scheme 5.4 Attempted synthesis of squaramide iminophosphorane catalyst and its hydrolysis.

Such instability of catalysts **467** and **470** led us to move forward with an investigation into the catalytic efficiency of the substituted iminophosphorane catalyst **464**, which was next evaluated in formal cycloaddition reactions between various anhydrides and benzaldehyde (Section 5.2.1).

5.3.1 Evaluation of catalyst 464

Under the conditions reported in the Table 5.3 we first tested catalyst **464** with 2-thiophenyl succinic anhydride (**425**) and benzaldehyde (**135**). Monitoring the reaction over time we observed higher reaction rates (entries 1-2, Table 5.3) than those observed with its unsubstituted analogue **459** (entries 1-4, Table 5.2). These results would support the hypothesis that the presence of electron-donating groups on the triarylphosphine moiety can increase the basicity of the catalyst, rendering it more capable of promoting the keto-enol equilibrium, and in turn increasing the rate of nucleophilic attack of the enol to the aldehyde.

Table 5.3 Kinetic studies in cycloaddition reaction between anhydride **425** and benzaldehyde.

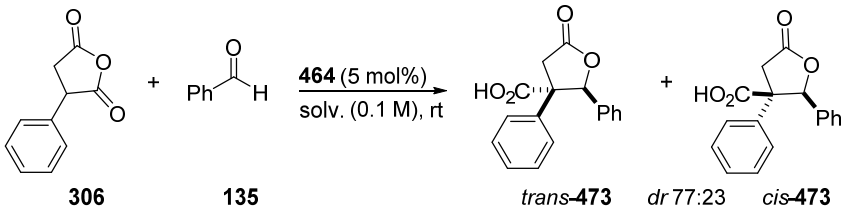


entry	time (h)	yield (%)[a]
1	18	4
2	32	12

[a]Yield of combined diastereomers determined by ^{1}H NMR spectroscopic analysis using *p*-iodoanisole as an internal standard.

Encouraged by these results, we then evaluated the catalytic performance of catalyst **464** in the formal cycloaddition between phenyl succinic anhydride (**306**) and benzaldehyde (**135**). This reaction was first attempted in the presence of squaramide derivative **200**, which yielded 44% of products *trans*-**473** and *cis*-**473** (90:10 *dr*) in 68% *ee* of the major diastereomer after 24 hours.[167]

Table 5.4 Kinetic studies on cycloaddition reaction between anhydride **306** and benzaldehyde (**135**)



entry	time (h)	yield (%)[a] using 464 in THF	time (h)	yield (%)[a] using 464 in MTBE
1	18	13	14	22
2	30	17	24	28
3	96	28	45	36
4	384	58	60	42

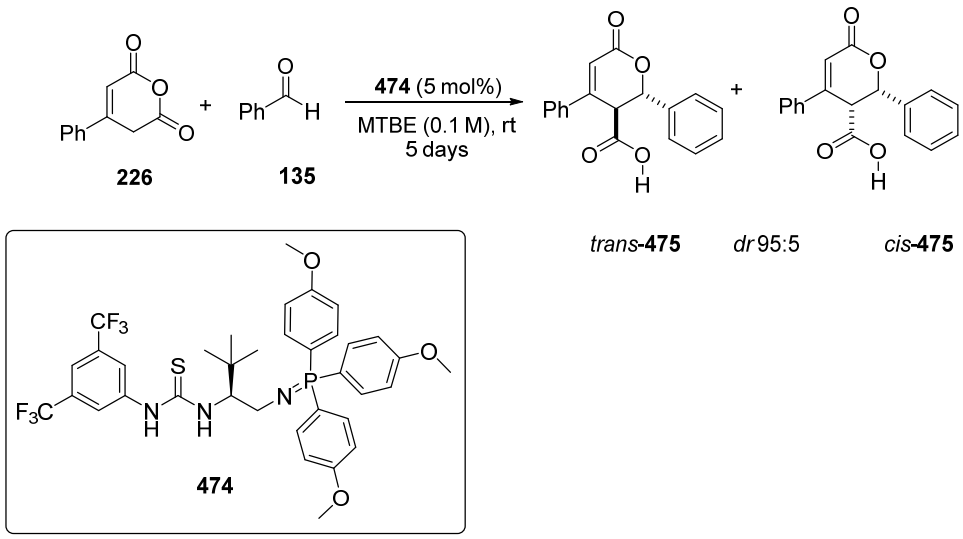
[a]Yield of combined diastereomers determined by ^{1}H NMR spectroscopic analysis using *p*-iodoanisole as an internal standard.

Unexpectedly, lower conversions after approximately the same period of time (entries 1 and 2, Table 5.4) were observed when iminophosphorane catalyst **464** was employed. However, repeating the same reaction in MTBE gave faster reactions than when performed in THF (comparison among entries 1-4, Table 5.4). Based on these results we decided to move forward with MTBE being our solvent of choice.

5.4 Evaluation of chiral catalyst 474

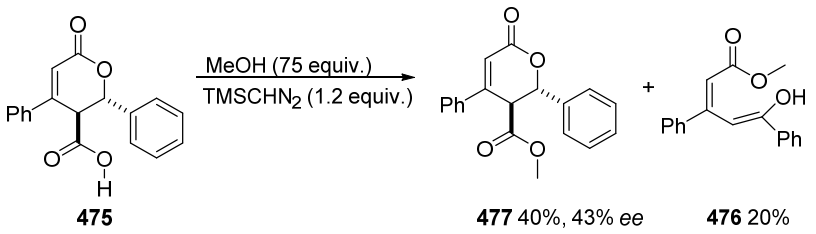
Despite relatively unsatisfactory results obtained up until this point, the kinetic studies previously reported had the merit of demonstrating the superiority of catalyst **464** over its unsubstituted analogue **459**. Thus, we went about the development of a chiral variant of this catalyst – successfully synthesised by Ms Astrid Botte and subsequently evaluated in collaboration with the author, in the cycloaddition reaction between anhydrides and a range of aldehydes.

In Section 4.7 we mentioned a failed attempt to develop a cycloaddition reaction between phenyl glutaconic anhydride (**226**) and benzaldehyde (**135**) promoted by trityl catalyst **326**. Gratifyingly, the employment of catalyst **474** in MTBE at room temperature promoted the reaction efficiently, affording **475** as a mixture of diastereomers in a ratio of 95:5 (Scheme 5.5).



Scheme 5.5 Catalytic cycloaddition reaction between phenyl glutaconic anhydride and benzaldehyde promoted by **474**.

The crude acid-lactones were then isolated by acidic/basic extraction and esterified under the conditions depicted in the Scheme below. Unfortunately this reaction generated the desired product *trans*-**477**, along with the side adduct **476**– most likely deriving from ring opening of the lactone by MeOH followed by decarboxylative elimination. Subsequent purification of **477** by column chromatography furnished *trans*-**477** with 43% *ee.*



Scheme 5.6 Esterification of *trans*-**475**.

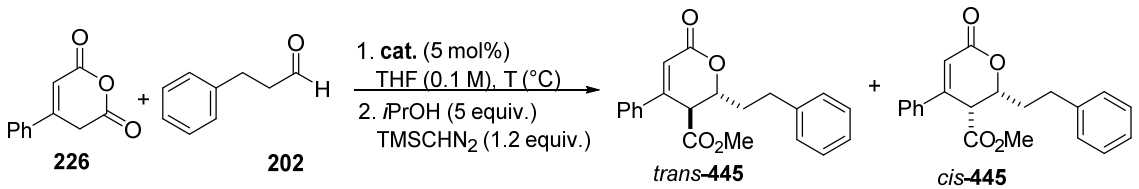
At this point in the study a collaborative effort began, focusing on the evaluation of superbase catalyst **474** with various aromatic (Ms Astrid Botte) and aliphatic aldehydes (author).

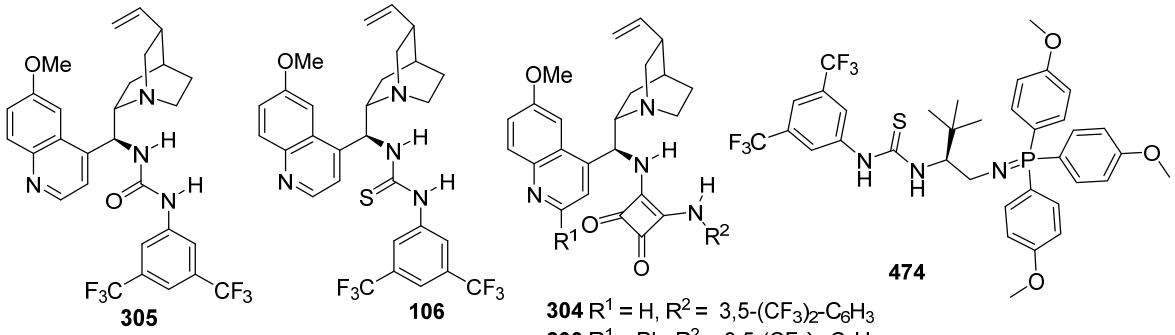
5.4.1 Evaluation of aliphatic aldehydes

In Sections 4.7.1 and 4.7.2 we reported some examples of asymmetric cycloaddition reactions between phenyl glutaconic anhydride and aliphatic aldehydes promoted by the trityl catalyst **326**. Although this methodology was tolerant of hindered *α*-branched aldehydes such as **403** (see Section 4.7.2, Chapter 4), inadequate levels of enantioselectivity were observed when linear aliphatic aldehydes such as hydrocinnamaldehyde were employed at lowered temperature. With the aim of improving the stereocontrol of this process, we decided to investigate the performance of a small library of catalysts, including chiral iminophosphorane **474** in the reaction between anhydride **226** and hydrocinnamaldehyde (**202**, Table 5.5) under the conditions found to be optimal in the preliminary studies conducted with the trityl catalyst **326** (see Table 4.2, Section 4.1.1, Chapter 4)

With the exception of (thio)urea catalysts **305** and **106** (entries 1 and 2), which failed to afford the corresponding products, all catalysts under evaluation promoted the reaction in low to moderate yield in convenient reaction times (entries 3-8). In contrast to what was observed with catalysts **304**, **200** and **228**, catalyst **474** furnished the product in moderate to good *dr* with a preference for the *trans*-isomer.

Table 5.5 Catalyst screening between phenyl glutaconic anhydride **226** and hydrocinnamaldehyde (**202**)





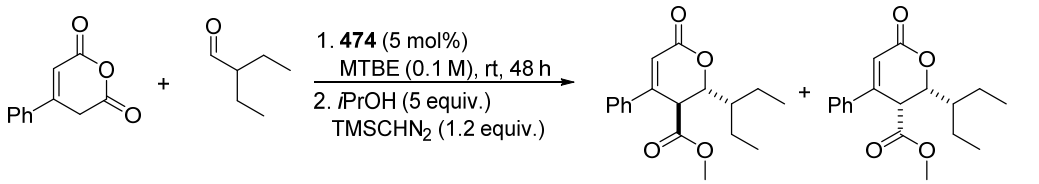
entry	cat.	loading (%)	T (°C)	solv.	time (h)	yield (%)[a]	*dr* (*cis:trans*)[b]	ee_{cis}(%)[c]	ee_{trans} (%)[c]
1	**305**	5	rt	THF	-	-	-	-	-
2	**106**	5	rt	THF	-	-	-	-	-
3	**304**	5	rt	THF	15	66	62:38	99	99
4	**304**	20	rt	THF	24	71	64:36	99	99
5	**200**	5	rt	THF	24	77	57:43	93	95
6	**228**	5	rt	THF	15	65	64:36	93	79
7	**474**	5	rt	THF	24	40	29:71	80	73
8	**474**	5	-15	THF	120	33	22:78	94	75

[a]Yield of combined diastereomers determined by ^{1}H NMR spectroscopic analysis using *p*-iodoanisole as an internal standard. [b]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis. [c]Determined by CSP-HPLC.

Analysis of the enantioselectivity of the reaction showed the *trans*-isomers of products were all formed in good *ee*, while the *cis*-isomers were always formed in *ee* ≥80%, and in particular near optical purity when catalyst **304** was employed (entries 3 and 4). Despite the reduced diastereocontrol provided by **304** and **200** (entries 3-5) compared to the other catalysts under examination (**228** and **474**), these two structures proved to be the most

efficient, promoting the only three reactions that achieved product *ee* above 90% in reasonable yield.

In analogy to these results, concomitant studies carried out by Ms Astrid Botte on the cycloaddition reaction involving phenyl glutaconic anhydride (**226**) and *α*-branched aldehyde **403** in the presence of catalyst **474** provided better *trans*-diastereo and enantioselectivity than that achieved with linear aldehydes such as **202**. (Scheme 5.7).



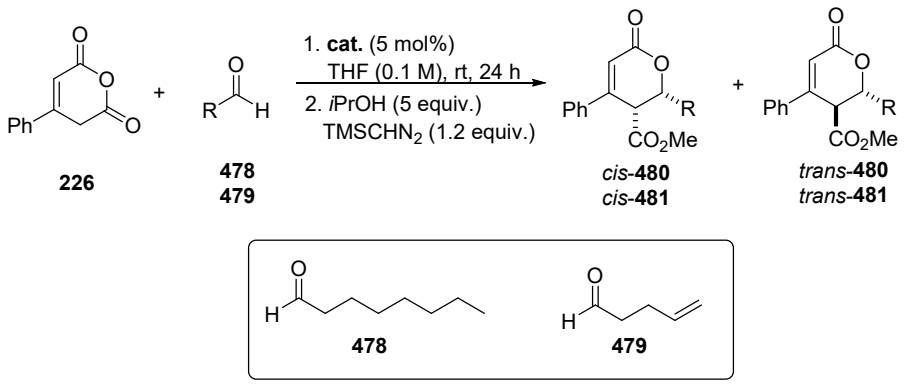
226 **403** *trans*-**447** 94% *ee* *dr* 76:24 *cis*-**447** 99% ee

Scheme 5.7 Cycloaddition reaction between anhydride **226** and aldehyde **403** promoted by **474**.

Based on these observations we hypothesised that the development of a highly enantioselective protocol involving either the linear or *α*-branched aldehydes could be possible by choice of an adequate catalyst. To test this, we conducted experiments involving commercially available linear aliphatic aldehydes **478** and **479**, which were previously successfully employed in asymmetric cycloaddition reactions with homophthalic anhydride (Table 4.3, Section 4.3, Chapter 4). Each aldehyde was evaluated in cycloaddition with phenyl glutaconic anhydride and both squaramide catalyst **304** and superbase catalyst **474** respectively. The results obtained are summarised in Table 5.7 below.

As expected, in both cases catalyst **304** (entries 1-3) formed a diastereomeric mixture of products **480** and **481** in a ratio of almost 1:1, with excellent enantiocontrol and higher yield than catalyst **474**. On the other hand catalyst **474** provided the product with moderate *trans*-diastereoselectivity - furnishing the *trans*-isomer in an enantiomeric excess of up to 95% (entries 2,4).

Table 5.7 Catalytic cycloaddition reactions involving aliphatic aldehyde **478** and **479**.

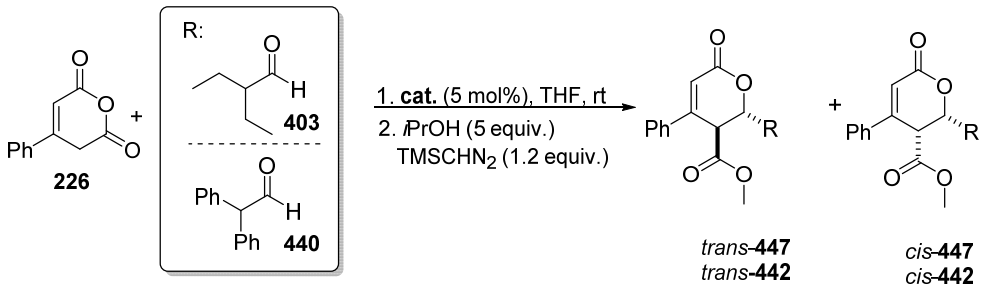


entry	catalyst	substrate	yield (%)[a]	*dr*(*cis*:*trans*)[b]	ee_{cis}(%)[c]	ee_{trans} (%)[c]
1	**304**	**478**	80	65:35	99	99
2[d]	**474**	**478**	42	25:75	30	94
3	**304**	**479**	81	56:44	99	99
4[d]	**474**	**479**	36	30:70	50	95

[a]Diastereomers not separable: combined isolated yield after column chromatography. [b]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis. [c]Determined by CSP-HPLC. [d]Experiment carried out by Ms Astrid Botte.

Hindered branched aromatic/aliphatic aldehydes (*e.g.* **403** and **440**) were also investigated in the presence of both catalysts. Consistent with previous results, iminophosphorane catalyst **474** provided the product with good diastereoselectivies, showing a preference for the *trans*-isomer, which was obtained in excellent to moderate *ee* (entries 1 and 3). Meanwhile, the use of a squaramide catalyst **304** reduced the *dr* to 1:1, delivering products in higher enantiomeric excesses (entries 2 and 4).

Table 5.8 Investigations into the cycloaddition between phenyl glutaconic anhydride **226** and aliphatic aldehydes.



entry	cat.	substrate	time (h)	yield (%)[a]	*dr(trans:cis)*[b]	ee_{trans} (%)[c]	ee_{cis} (%)[c]
1[d]	**474**	**403**	120	67	76:24	95	99
2	**304**	**403**	120	90	50:50	99	99
3[d]	**474**	**440**	24	42	87:13	66	-
4	**304**	**440**	24	90	52:48	99	99

[a]Diastereomers not separable: combined isolated yield after column chromatography. [b]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis. [c]Determined by CSP-HPLC. [d]Experiment carried out by Ms Astrid Botte.

5.5 Conclusion

This project has seen the synthesis and attempted synthesis of various novel bifunctional iminophosphorane catalysts. Kinetic studies carried out on the cycloaddition reaction between unreactive phenyl succinic anhydride derivatives and benzaldehyde allowed the identification of a substituted thiourea iminophosphorane derivative catalyst as a superior promoter of this transformation. We were also able to develop the first asymmetric cycloaddition reaction between phenyl glutaconic anhydride and benzaldehyde. An effort to expand the scope of this methodology with respect to the aldehydes component also demonstrated that hindered α-branched aldehyde were well tolerated.

6. General experimental data

Proton Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker DPX 400 MHz and Bruker Avance II 600MHz spectrometers, using as solvents $CDCl_3$, DMSO-d_6 or D_2O and referenced relative to residual $CHCl_3$ (δ = 7.26 ppm) DMSO (δ = 2.50 ppm) or H_2O (δ = 4.79 ppm). Chemical shifts are reported in ppm and coupling constants (*J*) in Hertz. Carbon NMR spectra were recorded on the same instruments (100 MHz) with total proton decoupling. Fluorine and phosphorus NMR spectra were recorded on the Bruker DPX400 machine (376.5 and 202 MHz respectively). HSQC, HMBC, NOE and ROESY NMR experiments were used to aid assignment of NMR peaks when required. All melting points are uncorrected. Infrared spectra were obtained using neat samples on a Perkin Elmer Spectrum 100 FT-IR spectrometer equipped with a universal ATR sampling accessory. ESI mass spectra were acquired using a Waters Micromass LCT- time of flight mass spectrometer (TOF), interfaced to a Waters 2690 HPLC. APCI experiments were carried out on a Bruker microTOF-Q III spectrometer interfaced to a Dionex UltiMate 3000 LC or direct insertion probe. The instrument was operated in positive or negative mode as required. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm. TLC analysis was performed on precoated $60F_{254}$ slides, and visualised by UV irradiation or $KMnO_4$ staining. Optical rotation measurements were made on a Rudolph Research Analytical Autopol IV instrument, and are quoted in units of 10^{-1} deg cm^2 g^{-1}. Anhydrous tetrahydrofuran (THF), CH_2Cl_2 and Et_2O were obtained by using Pure Solv MD4EN Solvent Purification System. Methanol (MeOH) was dried over activated 3Å molecular sieves. Commercially available anhydrous *t*-butyl methyl ether (MTBE), 1,4-dioxane, 2-methyltetrahydrofuran (2-MeTHF), 1,2-dimethoxyethane, diisopropyl ether were used. Analytical CSP-HPLC was performed on Daicel Chiralpak, AD, AD-H, IA, OD, OD-H, OJ-H (4.6 mm x 25 cm) and using ACQUITY UPC^2, Trefoil CEL1, CEL2, 2.5µm (3.0 x 150 mm). The X-ray intensity data for the crystal structure of *cis*-**364** was collected on a Bruker Smart Apex2 CCD diffractometer. A suitable crystal was selected and mounted using inert oil on a 0.3mm MiTeGen loop and placed on the goniometer head in a 100K N_2 gas stream. The dataset was collected using Bruker APEX2 v2011.8-0 software. Data integrations, reductions and corrections for absorption and polarization effects were all performed using APEX2 v2011.8-0 software. Space group determination, structure solution and refinement were obtained using Bruker Shelxtl*

Ver. 6.14 software. The structures were solved with Direct Methods using the SHELXTL program and refined against IF^2I with the program XL from SHELX-97 using all data. Non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were placed into geometrically calculated positions and refined using a riding model. (*Software Reference Manual, version 5.625; Bruker Analytical X-Ray Systems Inc.: Madison, WI, 2001. Sheldrick, G. M. SHELXTL, An Integrated System for Data Collection, Processing, Structure Solution and Refinement; Bruker Analytical X-Ray Systems Inc.: Madison, WI, 2001).

6.1 Experimental procedures and data for Chapter 2

6.1.1 Racemic preparation of dihydroisocoumarins 302

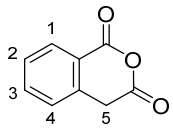
An oven-dried 10 mL round-bottomed flask containing a magnetic stirring bar under an argon atmosphere was charged with homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). Anhydrous MTBE (2.5 mL, 0.1 M) was added *via* syringe followed by **289** (46.8 mg, 0.246 mmol). *N*,*N*-Diisopropylethylamine (8.6 μL, 0.0495 mmol - 20 mol%) was added *via* syringe and the resulting mixture was allowed to stir for 20 h at room temperature. The corresponding carboxylic acids were dissolved in dry MTBE (0.1 M) and anhydrous MeOH (75 equiv.), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 1.2 equiv.) were added *via* syringe and the reaction was allowed to stir for 30 min at room temperature. The solvent was then removed *in vacuo* and the crude mixture of diastereomeric esters was purified by flash column chromatography, (hexanes/EtOAc 8:2) to afford both diastereomers.

6.1.2 General procedure A: organocatalysed cycloaddition reaction between homophthalic anhydride (147) and Michael acceptors (285) and (289) (Table 2.1, entry 5 and Table 2.4, entry 4)

An oven-dried 10 mL round-bottomed flask containing a magnetic stirring bar under an argon atmosphere was charged with homophthalic anhydride (**147**, 1 equiv.) and catalyst **200** or **305** (5 mol%). Anhydrous MTBE (0.1 M) was added *via* syringe followed by the relevant Michael acceptors (1 equiv.) and the resulting mixture was allowed to stir under the reaction conditions (time and temperature) indicated in Table 2.1. The yield and diastereomeric ratio of the carboxylic acid were determined by ^{1}H NMR spectroscopic analysis using *p*-iodoanisole (0.5 equiv.) as an internal standard. The corresponding

carboxylic acid was then dissolved in dry MTBE (0.1 M) and anhydrous MeOH (75 equiv.), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 1.2 equiv.) were added *via* syringe. The reaction was allowed to stir for 1 h at room temperature. The solvent was then removed *in* vacuo and the corresponding diastereomeric ester was purified by flash column chromatography (hexanes/EtOAc 8:2) to afford the *trans*-diastereomer **302** or **303**. The enantiomeric excess of the *trans*-**302** was determined by CSP-HPLC.

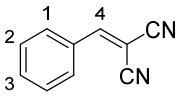
Homophthalic anhydride (**147**)[222]



A 50 mL round-bottomed flask containing a magnetic stirring bar was charged with homophthalic acid (**298**, 2.00 g, 11.1 mmol). Acetic anhydride (25 mL) was added, the flask was fitted with a condenser and the reaction mixture was heated at 80 °C for 2 h. The excess acetic anhydride was removed *in vacuo* and the solid obtained was triturated with Et_2O (10 mL), filtered and dried to obtain homophthalic anhydride (**147**) as an off white solid (1.50 g, 85%). M.p. 141-142 °C (lit.,[222] m.p. 143-144 °C).

δ_H (400 MHz, DMSO-d_6): 8.05 (1 H, d, *J* 7.8, H-1), 7.75 (1 H, app. t, *J* 7.8, H-2), 7.52 (1 H, app. t, *J* 7.8, H-3), 7.44 (1 H, d, *J* 7.8, H-4), 4.28 (2 H, s, H-5).

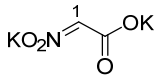
2-Benzylidene-malononitrile (**282**)[211]



A mixture of benzaldehyde (**135**, 960 μL, 9.40 mmol) and malonitrile (**281**, 933 mg, 14.1 mmol) was ground at room temperature in a glass mortar for 1h. The mixture was taken up in H_2O (15 mL) and stirred for 15 min. The resulting solid was collected by suction filtration and dried to afford **282** as a brown solid (850 mg, 66%). M.p. 79-81 °C (lit.,[212] m.p. 87-88 °C).

δ_H (400 MHz, $CDCl_3$): 7.88 (2 H, d, *J* 7.5, H-1), 7.76 (1 H, s, H-4), 7.67-7.60 (1 H, app. t, *J* 7.5, H-3), 7.50-7.54 (2 H, app. t, *J* 7.5, H-2).

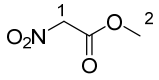
Dipotassium nitroacetate (283)[212]



A 100 mL three necked round-bottomed flask equipped with a condenser and a magnetic stirring bar was charged with KOH (4.48 g, 80.0 mmol) and H_2O (12.1 mL). The reaction mixture was heated at 70 °C and nitromethane (**103**, 2.8 mL, 52.4 mmol) was slowly added dropwise *via* syringe. After completion of the addition, the stirring was stopped and the reaction was warmed to 160 °C for 1 hour. The resulting solution was allowed to cool to room temperature, the precipitate formed was filtered through a sintered glass frit, washed with methanol (3 × 75 mL) and dried *in vacuo* to furnish **283** as a peach powder (3.20 g, 82%). M.p. 240-242 °C, (lit.,[212] m.p. 242-243 °C).

δ_H (400 MHz, $CDCl_3$): 4.64 (1 H, s, H-1).

Methyl 2-nitroacetate (284)[213]

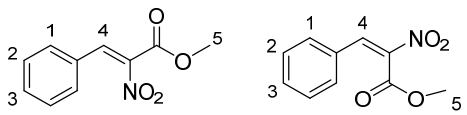


A 100 mL three necked round-bottomed flask equipped with a stirring bar and a calcium chloride drying tube was charged with **283** (5.00 g, 27.0 mmol) and MeOH (33 mL). The reaction mixture was cooled to -15 °C and conc. H_2SO_4 (15 mL) was added over approximately 1 h. The mixture was warmed to room temperature and stirred for 8 h. The precipitate formed was removed by suction filtration and the filtrate concentrated under *vacuo*. The residual oil was then dissolved in CH_2Cl_2 and washed with water. The organic phases were collected, dried over anhydrous $MgSO_4$, filtered and concentrated to furnish **284** as a yellow oil (1.90 g, 59%).

δ_H (400 MHz, $CDCl_3$): 5.31 (2 H, s, H-1), 2.32 (3 H, s, H-2).

HRMS (*m/z* - ESI): $[M]^+$ Found: 119.0223 $C_3H_5NO_4$ Requires: 119.0219.

(*Z*/*E*) Methyl 2 nitro-3-phenylacrylate (285)[213]



(*Z*)-**285** (*E*)-**285**

An oven-dried 50 mL round-bottomed flask containing a magnetic stirring bar under an argon atmosphere was charged with **284** (1.20 g, 10.1 mmol), benzaldehyde (**135**, 1.5 mL, 15.0 mmol) and dry THF (25 mL). The reaction mixture was cooled to -10 °C and $TiCl_4$ (17 mL, 17.0 mmol) followed by *N*-methylmorpholine (4.3 mL, 40.0 mmol) were added dropwise *via* syringe. The reaction was allowed to warm to room temperature, stirred for 18 h and then diluted with H_2O (15 mL). The mixture was extracted with CH_2Cl_2 (3 x 10 mL), the combined organic layers were then dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was then purified by flash column chromatography eluting with 80:20 hexanes:EtOAc, to furnish **285** as a mixture of (*Z/E*)-diastereomers in a 55:45 ratio (621 mg, 30%).

(*Z*)-**285**:

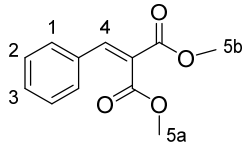
δ_H (400 MHz, $CDCl_3$): 8.11 (1 H, s, H-4), 7.52-7.47 (5 H, m, H-1, H-2, H-3), 3.93 (3 H, s, H-5).

(*E*)-**285**:

δ_H (400 MHz, $CDCl_3$): 7.56 (1 H, s, H-4), 7.52-7.47 (5 H, m, H-1, H-2, H-3), 3.97 (3 H, s, H-5).

HRMS (*m/z* - ESI): $[M]^+$ Found: 207.0534 $C_{10}H_9NO_4$ Requires: 207.0531.

Dimethyl 2-benzylidenemalonate (288)[214]

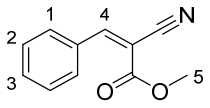


A 50 mL round-bottomed flask equipped with a reflux condenser and containing a magneting stirring was charged with benzaldehyde (**147**, 2.0 mL, 19.0 mmol) and dimethylmalonate (**286**, 2.2 mL, 19.0 mmol). CH_2Cl_2 (20 mL) was added followed by 10

mol% of piperidine (375 μL, 3.80 mmol) and the reaction mixture was heated at reflux temperature for 4 h. The solvent was then removed under reduced pressure and the residue purified by column chromatography on silica gel, eluting with 70:30 hexanes:EtOAc, to afford **288** as white crystalline solid (2.82 g, 67%). M.p. 32-33 °C, (lit.,[214] m.p. 27-28 °C).

δ_H (400 MHz, $CDCl_3$): 7.76 (1 H, s, H-4), 7.42-7.36 (5 H, m, H-1, H-2, H-3), 3.84 (6 H, s, H-5a and H-5b).

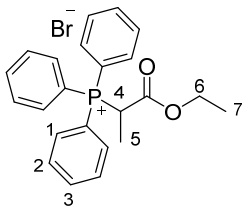
(*Z*)-2-Cyano-3-phenyl-acrylic acid methyl ester (289)[214]



A 50 mL round-bottomed flask equipped with a reflux condenser and containing a magnetic stirring was charged with benzaldehyde (**135**, 1.0 mL, 10.0 mmol) and methylcyanoacetate (**287**, 882 μL, 10.0 mmol). CH_2Cl_2 (25 mL) was added followed by 10 mol% of piperidine (118 μL, 1.20 mmol) and the reaction was heated at reflux temperature for 4 h. The solvent was then evaporated *in vacuo* to furnish a yellow solid that was purified by recrystallisation from Et_2O to afford **289** as yellow solid (1.50 g, 82%). M.p. 84-85 °C, (lit.,[214] m.p. 83-84 °C).

δ_H (400 MHz, $CDCl_3$): 8.39 (1 H, s, H-4), 8.03 (2 H, d, *J* 7.2 , H-1), 7.55-7.64 (3 H, m, H-2, H-3), 3.84 (3 H, s, H-5).

(1-ethoxy-1-oxopropan-2-yl)triphenylphosphonium (292)[223]

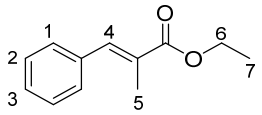


A 100 mL round-bottomed flask fitted with a condenser and containing a magnetic stirring bar was charged with triphenylphosphine (**291**, 7.20 g, 27.6 mmol) and toluene (50 mL). Ethyl 2-bromo proponiate (**290**, 3.5 mL, 27.6 mmol) was then added *via* syringe and the resulting white suspension was heated at 90 °C for 16 h. The mixture was then cooled to room temperature and the solid formed was isolated by suction filtration,

washed with Et_2O (2 × 25 mL) and dried to give **292** as a white solid (10.0 g, 82%). M.p. 150-152°C, (lit.,[223] m.p. 153-156 °C).

δ_H (400 MHz, $CDCl_3$): 8.05-7.90 (6 H, m, H-1), 7.78-7.68 (3 H, m, H-3), 7.68-7.64 (6 H, m, H-2), 7.27-7.18 (1 H, m, H-4), 3.99 (2 H, q, *J* 7.1, H-6), 1.69 (3 H, dd, *J* 7.1, 18.5, H-5), 1.00 (3 H, t, *J* 7.1, H-7).

(*E*)-Ethyl 2-methyl-3-phenylacrylate (294)[224]

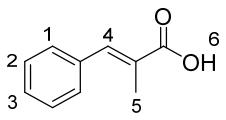


A 250 mL round-bottomed flask containing a magnetic stirring bar was charged with **292** (10.0 g, 22.5 mmol) and CH_2Cl_2(80 mL) followed by an aqueous solution of NaOH (1.0 M, 80 mL). The reaction was allowed to stir vigorously at room temperature for 15 min after which time the organic layer was discarded and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford a residue containing the corresponding crude ylide (**293**, 9.33 g, 93%) which was dissolved in toluene (14 mL). and transferred *via* syringe to a 100 mL round-bottomed flask containing a magnetic stirring bar. To the mixture was added freshly distilled benzaldehyde (**135**, 2.6 mL, 26.1 mmol) and the reaction was allowed to stir at room temperature for overnight. The solvent was then removed under reduced pressure and the residue obtained was purified by flash column chromatography, eluting with 90:10 hexanes:EtOAc, to give **294** as a yellow pale oil (4.40 g, 89%).

δ_H (400 MHz, $CDCl_3$): 7.69 (1 H, s, H-4), 7.41-7.33 (4 H, m, H-1 and H-2), 7.32-7.25 (1 H, m, H-3), 4.25 (2 H, q, *J* 6.8, H-6), 2.10 (3 H, s, H-5), 1.33 (3 H, t, *J* 6.8, H-7).

HRMS (*m/z* - ESI): $[M+H]^+$ Found: 191.1058 $C_{12}H_{15}NO_2$ Requires: 191.1066.

(*E*)-Ethyl 2-methyl-3-phenylacrylate (**295**)[225]

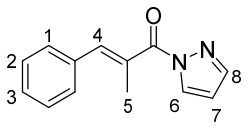


To a solution of **294** (905 mg, 4.75 mmol) in EtOH (12 mL), was added a 10% aqueous solution of NaOH (26 mL) and the resulting reaction mixture was allowed to stir at room temperature for 12 h. The mixture was then acidified to pH =1.0 by addition of an aqueous solution of HCl (1.0 M, 25 mL) and extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford the corresponding product **295** as a white solid (753 mg, 95%). M.p. 75-77°C (lit.,[225] m.p. 78-80 °C).

δ_H (400 MHz, $CDCl_3$): 7.81 (1 H, s, H-4), 7.47-7.36 (4 H, m, H-1 and H-2), 7.36-7.30 (1 H, m, H-3), 2.13 (3 H, s, H-5).

* The protic signal (H-6) is not visible in $CHCl_3$

(*E*)-2-methyl-3-phenyl-1-(pyrazol-1-yl)prop-2-en-1-one (**296**)



To a stirred solution of pyrazole (**297**, 333 mg, 4.90 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added **295** (735 mg, 4.50 mmol) followed by DMAP (54.9 mg, 0.45 mmol) and DCC (1.38 g, 6.70 mmol). The reaction mixture was stirred at 0 °C for 10 min and then allowed to warm to room temperature for 48 h. The suspension was then filtered and the precipitate washed with CH_2Cl_2. The filtrate was washed with a saturated aqueous solution of $NaHCO_3$ (25 mL), dried over Na_2SO_4 and concentrated under reduce pressure to furnish a pale yellow oil. The crude product was then purified by flash column chromatography, eluting with 70:30 hexanes:EtOAc, to give **296** as a white solid (250 mg, 26%). M.p: 60-62°C.

δ_H (400 MHz, $CDCl_3$): 8.31 (1 H, dd, *J* 0.7, 2.8, H-6), 7.73 (1 H, dd, *J* 0.7, 1.5, H-8), 7.54 (1 H, q, *J* 1.4, H-4), 7.48-7.41 (2 H, m, H-1), 7.40-7.34

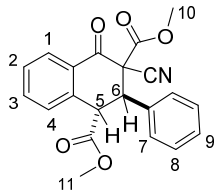
(2 H, m, H-2), 7.33-7.27 (1 H, m, H-3), 6.46 (1 H, dd, *J* 1.5, 2.8, H-7), 2.32 (3 H, d, *J* 1.4, H-5).

δ_C (100 MHz, $CDCl_3$): 163.3 (C=O), 160.4, 143.4, 142.1, 129.6, 128.5, 128.4, 126.7, 114.8, 109.4, 19.0.

ν_{max} (neat)/cm^{-1}: 3675, 2970, 2622, 1664, 1447, 1415, 1200, 1128, 1003, 797.

HRMS (*m/z* - ESI): $[M+Na]^+$ Found: 235.0846 $C_{13}H_{12}N_2ONa$ Requires: 235.0847.

3-Cyano-4-oxo-2-phenyl-1,2,3,4-tetrahydronaphthalene-1,3-dicarboxylic acid dimethyl ester (*trans*-**302**, Table 2.4, entry 4)



Synthesised according to general procedure A by reaction of anhydride **147** (39.9 mg, 0.246 mmol), catalyst **304** (7.75 mg, 0.0123 mmol - 5 mol%) and Michael acceptor **289** (46.0 mg, 0.246 mmol) at -30 °C for 97 h After purification by flash column chromatography with 80:20 hexanes:EtOAc, *trans*-**302** was isolated as a yellow solid (10.0 mg, 11%, 30% *ee*). M.p. 148-150 °C, $[\alpha]_D^{20}$ = -14.0 (*c* = 4.3, $CHCl_3$).

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 80/20, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: *trans*-**302** 17.2 min (major enantiomer) and 19.0 min (minor enantiomer).

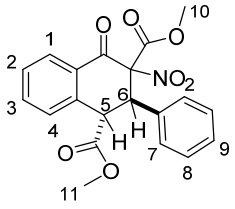
δ_H (400 MHz, $CDCl_3$): 8.15 (1 H, d, *J* 7.6, H-1), 7.67 (1 H, app. t, *J* 7.6, H-2), 7.52-7.47 (3 H, m, H-3, H-4, H-9), 7.38-7.32 (4 H, m, H-7 and H-8), 4.87 (1 H, d, *J* 12.1, H-6), 4.40 (1 H, d, *J* 12.1, H-5), 3.74 (3 H, s, H-10), 3.60 (3 H, s, H-11).

δ_C (100 MHz, $CDCl_3$): 184.0 (C=O), 170.8 (C=O), 164.0 (C=O), 139.0, 136.0, 134.3, 129.8, 129.2, 129.0, 128.9, 128.5, 128.1, 127.4, 113.3, 61.4, 53.9, 52.6, 49.2, 48.5.

ν_{max} (neat)/cm^{-1}: 2215, 1743, 1689, 1596, 1440, 1338, 1249, 1227, 949, 882, 754, 665.

HRMS (*m/z* - ESI): $[M+H]^+$ Found: 364.1179 $C_{21}H_{18}NO_5$ Requires: 364.1185.

3-Nitro-4-oxo-2-phenyl-1,2,3,4-tetrahydro-naphthalene-1,3-dicarboxylic acid dimethyl ester (*trans*-**303**, Table 2.1, entry 5)



Synthesised according to general procedure A by reaction of anhydride **147** (39.9 mg, 0.246 mmol), catalyst **200** (8.70 mg, 0.0123 mmol – 5 mol%) and Michael acceptor **285** (51.0 mg, 0.246 mmol) at rt for 72 h. After purification by flash column chromatography eluting with 80:20 hexanes:EtOAc, *trans*-**303** was isolated as a white oil (20.2 mg, 20%); $[\alpha]_D^{20}$ = -1.02 (*c* =0.3 $CHCl_3$).

δ_H (400 MHz, $CDCl_3$): 8.12 (1 H, d, *J* 7.8, H-1), 7.69 (1 H app. t, *J* 7.8, H-2), 7.55 (1 H, app. t, *J* 7.8, H-3), 7.52-7.47 (2 H, m, H-7), 7.40-7.32 (4 H, m, H-4, H-8, H-9), 4.91 (1 H, d, *J* 12.1, H-6), 4.70 (1 H, d, *J* 12.1, H-5), 3.79 (3 H, s, H-10), 3.56 (3 H, s, H-11)

δ_C (100 MHz, $CDCl_3$): 183.0 (C=O), 170.8 (C=O), 161.7 (C=O), 138,8, 135.5, 132.4, 130.4, 129.5, 129.1, 128.9, 128.3, 127.2, 101.0, 53.9, 52.7, 49.6, 49.0, 29.7.

ν_{max} (neat)/cm^{-1}: 2937, 1759, 1734, 1564, 1497, 1287, 1259, 1221, 1106, 903, 885, 760.

HRMS (*m/z* - ESI): $[M]^+$ Found: 383.1005 $C_{20}H_{17}NO_7$ Requires: 383.1005.

6.2 Experimental procedures and data for Chapter 3

6.2.1 General procedure B: Synthesis of aldehydes 314 and 329 from aryl methyl ketones 312 and 332 *via* epoxides 313 and 333 as precursors

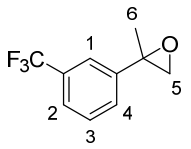
An oven-dried 100 mL round-bottomed flask containing a magnetic stirring bar under an argon atmosphere and fitted with a reflux condenser was charged with NaH (60% in mineral oil, 240 mg, 6.00 mmol). Anhydrous THF (4 mL) was added *via* syringe followed by trimethylsulfoxonium iodide (1.40 g, 6.00 mmol) and the reaction mixture was stirred at 70 °C for 1 h. A solution of aryl methyl ketone (**312** or **332**, 3.00 mmol) in dry THF (4 mL) was then added *via* syringe and the reaction mixture was left stirring for an additional 48 h at 70 °C. The reaction mixture was then diluted with H_2O (10 mL), extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude product which was purified by flash column chromatography eluting with 90:10 hexanes:EtOAc to isolate epoxide **313** or **333** respectively. A solution of the relevant epoxide (2.90 mmol) in dry THF (8 mL), was subsequently added *via* syringe to an oven-dried round-bottomed flask containing a magnetic stirring bar under an argon atmosphere and the solution was cooled to 0 °C. $BF_3{\cdot}Et_2O$ (468 µL, 3.80 mmol) was added *via* syringe and the reaction mixture was stirred for 24 h at rt, then diluted with a 5% aqueous solution of NaH_2PO_4 (10 mL), and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo* to afford the crude product which was purified by flash column chromatography eluting with 90:10 hexanes:EtOAc, to give the corresponding aldehyde **314** or **329**.

6.2.2 Genaral procedure C: Synthesis of aldehydes 330 and 331 from ketones 334 and 335 *via* enol-methyl ether 336 and 337 as precursors

An oven-dried 100 mL round-bottomed flask containing a magnetic stirring bar under an argon atmosphere was charged with $Ph_3PCH_2OCH_3Cl$ (1.70 g, 5.00 mmol) and anhydrous THF (20 mL). The mixture was then cooled to 0 °C and *t*BuOK (594 mg, 5.30 mmol) was subsequently added portionwise. After 30 min a solution of ketone **334** or **335** (3.37 mmol) in dry THF (20 mL) was added dropwise *via* syringe to the reaction mixture which was stirred at 0 °C for 30 min and then allowed to warm to room temperature. The reaction was then poured into water (20 mL) and extracted with EtOAc (3 x 10 mL). The combined

organic layers were dried over anhydrous $MgSO_4$ and then concentrated under reduced pressure to afford the crude product enol-methyl ether product **336** or **337** respectively, which was purified by flash column chromatography. The relevant pure enol-methyl ether **336** or **337**, was then dissolved in Et_2O (20 mL) and a 70% aqueous solution of $HClO_4$ (5 mL) was slowly added. After 24 h the mixture was diluted with a saturated aqueous solution of $NaHCO_3$ (20 ml) and the organic phase was extracted with Et_2O, dried over anhydrous $MgSO_4$ and the solvent removed *in vacuo*. Then the residue was purified by flash column chromatography to afford the corresponding *α*-arylaldehyde **330** or **331**.

2-Methyl-2-(3-trifluoromethyl-phenyl) oxirane (313)[226]

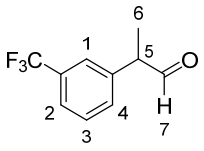


Prepared according to general procedure B by reaction of 3-(trifluoromethyl) acetophenone (**312**, 2.00 g, 10.6 mmol) with NaH (60% in mineral oil, 800 mg, 21.2 mmol) and $Me_3S(O)I$ (2.00 g, 21.2 mmol) in anhydrous THF (20 mL) at 70 °C. Upon purification by flash column chromatography, eluting with 90:10 hexanes:EtOAc, epoxide **313** was obtained pure as yellow oil (1.40 g, 65%).

δ_H (400 MHz, $CDCl_3$): 7.61-7.39 (4 H, m, H-1, H-2, H-3, H-4), 2.96 (1 H, d, *J* 5.4 Hz, H-5a), 2.73 (1 H, d, *J* 5.4, H-5b), 1.71 (3 H, s, H-6)

HRMS (*m/z* - ESI): $[M+Na]^+$ Found: 225.1560 $C_{10}H_9F_3ONa$ Requires: 225.1563.

2-(3 trifluoromethyl-phenyl)-propionaldehyde (314)[226]

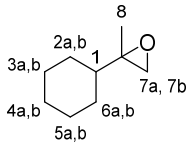


Prepared according to general procedure B by reaction of epoxide **313** (1.40 g, 6.90 mmol) with BF_3•Et_2O (1.1 mL, 9.10 mmol) in dry THF (20 mL) at room temperature for 24 h. Purification of the crude product by flash column chromatography eluting with 90:10 hexanes:EtOAc, furnished the pure aldehyde **314** as a pale yellow oil (503 mg, 35%).

δ_H (400 MHz, $CDCl_3$): 9.68 (1 H, s, H-7), 7.58-7.33 (4 H, m, H-1, H-2, H-3, H-4), 3.70 (1 H, q, *J* 7.2, H-5), 1.47 (3 H, d, *J* 7.2, H-6).

HRMS (*m/z* - ESI): $[M+H]^+$ Found: 203.0604 $C_{10}H_{10}F_3O$ Requires: 203.0605.

2-Cyclohexyl-2-methyloxirane (**333**)[226]

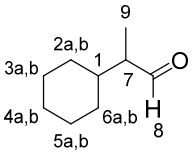


Prepared according to general procedure B by reaction of 1-cyclohexylethanone (**332**, 1.1 mL, 8.00 mmol) with NaH (60% in mineral oil, 640 mg, 16.0 mmol) and $Me_3S(O)I$ (3.70 g, 16.0 mmol) in anhydrous THF (20 mL) at 70 °C. Upon purification by flash column chromatography eluting with 90:10 hexanes:EtOAc, epoxide **333** was obtained pure as a colourless oil (340 mg, 30%).

δ_H (400 MHz, $CDCl_3$): 2.20 (1 H, d, *J* 5.4, H-7a), 2.11 (1 H, d, *J* 5.4, H-7b) 1.50-1.29 (5 H, m, H-2a, H-3a, H-4a, H-5a, H-6a), 0.96-0.46 (6 H, m, H-1, H-2b, H-3b, H-4b, H-5b, H-6b), 0.87 (3 H, s, H-8).

HRMS (*m/z* - ESI): $[M]^+$ Found: 140.1101 $C_9H_{16}O$ Requires:140.1201.

2-Cyclohexylpropanal (**329**)[226]



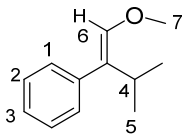
Prepared according to general procedure B by reaction of epoxide **333** (600 mg, 4.60 mmol) with BF_3•OEt (250 µL, 2.00 mmol) in dry THF (10 mL) at room temperature for 24 h. Purification of the crude product by flash column chromatography eluting with 90:10 hexanes:EtOAc, furnished the pure aldehyde **329** as a colourless oil (36.0 mg, 58%).

δ_H (400 MHz, $CDCl_3$): 9.56 (1 H, d, *J* 2.3, H-8), 2.28-2.09 (1 H, m, H-7) 1.83-1.49 (5 H, m, H-2a, H-3a, H-4a, H-5a, H-6a), 1.30-0.74 (6 H, m,

H-1, H-2b, H-3b, H-4b, H-5b, H-6a), 0.95 (3 H, d, *J* 7.0, H-9).

HRMS (*m/z* - ESI): $[M+H]^+$ Found: 141.1101 $C_9H_{17}O$ Requires: 141.1201.

(1-Methoxymethylene-2methyl-propyl)-benzene (336)[227]

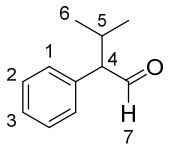


Prepared according to procedure C by reacting isobutyrophenone (**334**, 500 g, 3.40 mmol) with $Ph_3PCH_2OCH_3Cl$ (1.70 g, 5.00 mmol) and *t*BuOK (594 mg, 5.30 mmol) in anhydrous THF (20 mL). Upon purification by flash column chromatography, eluting with 85:15 hexanes:EtOAc, the enol ether **336** was obtained pure as a yellow oil (210 mg, 35%).

δ_H (400 MHz, $CDCl_3$): 7.29-7.20 (5 H, m, H-1, H-2, H-3), 5.94 (1 H, s, H-6), 3.65 (3 H, s, H-7), 3.05 (1 H, sept., *J* 7.3, H-4), 1.14 (6 H, d, *J* 7.3, H-5).

HRMS (*m/z* - ESI): $[M+H]^+$ Found: 177.2588 $C_{12}H_{17}O$ Requires: 177.2590.

3-Methyl 2-phenyl butanal (330)[227]

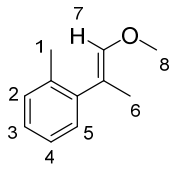


Prepared according to procedure C, by reacting the enol ether **336** (210 mg, 1.20 mmol) with a 70% aqueous solution of $HClO_4$ (2 mL) in Et_2O (10 mL). Purification of the crude product by flash column chromatography, eluting with 90:10 hexanes:EtOAc, afforded the pure aldehyde **330** as a white oil (120 mg, 57%).

δ_H (400 MHz, $CDCl_3$): 9.69 (1 H, d, *J* 3.2, H-7), 7.37-7.13 (5 H, m, H-1, H-2, H-3), 3.17 (1 H, dd, *J* 3.2, 9.5, H-4), 2.46-2.33 (1 H, m, H-5), 1.03 (6 H, d, *J* 6.7, H-6).

HRMS (*m/z* - ESI): $[M+H]^+$ Found: 163.1124 $C_{11}H_{15}O$ Requires: 163.1123.

1-(2-Methoxy-1-methyl-vinyl)-2-methyl-benzene (337)[227]

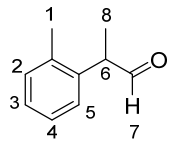


Prepared according to general procedure C by reacting 2-methylacetophenone (**335**, 2 mL, 15.0 mmol) with $Ph_3PCH_2OCH_3Cl$ (7.60 g, 22.5 mmol) and *t*BuOK (2.70 g, 24.0 mmol) in anhydrous THF (40 mL). Upon purification by flash column chromatography, eluting with 80:20 hexanes:EtOAc, the enol ether **337** was obtained pure as a colourless oil (1.10 g, 45%).

δ_H (400 MHz, $CDCl_3$): 7.37-7.14 (4 H, m, H-2, H-3, H-4 and H-5), 5.96 (1 H, s, H-7), 3.70 (3 H, s, H-8), 2.35 (3 H, s, H-1), 1.94 (3 H, s, H-6).

HRMS (*m/z* - ESI): $[M+H]^+$ Found: 163.1085 $C_{12}H_{15}O$ Requires:163.1085.

2-(o-Tolyl)propanal (331)[227]

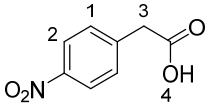


Prepared according to general procedure C by reacting enol ether **337** (1.10 g, 6.78 mmol) with a 70% aqueous solution of $HClO_4$ (2 mL) in Et_2O (10 mL) at room temperature for 24 h. Purification of the crude product by flash column chromatography, eluting with 90:10 hexanes:EtOAc, afforded the pure aldehyde **331** as a yellow oil (350 mg, 35%).

δ_H (400 MHz, $CDCl_3$): 9.65 (1 H, d, *J* 1.2, H-7), 7.17-7.24 (3 H, m, H-3, H-4, H-5), 7.03-7.06 (1 H, m, H-2), 3.83 (1 H, dq, *J* 1.2, 6.8, H-6), 2.35 (3 H, s, H-1), 1.40 (3 H, d, *J* 6.8, H-8).

HRMS (*m/z* - ESI): $[M-H]^-$ Found: 147.0814 $C_{10}H_{11}O$ Requires: 147.0810.

4-Nitrophenyl acetic acid (316)[228]

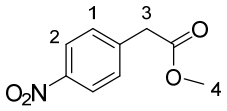


A 50 mL round-bottomed flask containing a magnetic stirring bar was charged with 4-nitrophenyl acetonitrile (**315**, 5.00 g, 30.8 mmol), water (11 mL) followed by conc. H_2SO_4 (6 mL) and glacial acetic acid (6 mL). The resulting reaction mixture was heated at reflux temperature for 2 h and then cooled to 0 °C. The precipitate formed was filtered off, washed with water (30 mL) and dry to afford the product **316** as a white solid (5.58 g, 98%). M.p 153-155°C (lit[228] m.p. 153-155 °C).

δ_H (400 MHz, DMSO): 8.15 (2 H, d, *J* 8.6, H-2), 7.52 (2 H, d, *J* 8.6, H-1), 3.75 (2 H, s, H-3).

*The protic signal (H-4) is not visible in $CHCl_3$

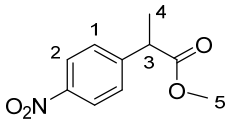
4-Nitrophenyl acetic ester (**317**)[229]



In a 50 mL round-bottomed flask containing a magnetic stirring bar nitroacetic acid (**316**, 5.58 g, 30.8 mmol), was dissolved in MeOH (20 mL) and conc. H_2SO_4 (5 mL). The resulting solution was then heated at 80 °C for 4 h and then cooled to room temperature. An aqueous solution of NaOH (2.0 M, 50 mL) was added and the reaction mixture was then extracted with EtOAc (2 x 40 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and the volatiles were removed under reduced pressure to afford **317** as pale yellow solid (3.66 g, 61%). M.p 45-50 °C (lit[229] m.p. 46-47 °C).

δ_H (400 MHz, $CDCl_3$): 8.13 (2 H, d, *J* 8.3, H-2), 7.43 (2 H, d, *J* 8.3, H-1), 3.73 (2 H, s, H-3), 3.68 (3 H, s, H-4).

2-(4-Nitro-phenyl)-propionic acid methyl ester (**318**)[215]



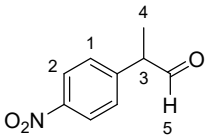
To a stirred solution of **317** (537 mg, 2.75 mmol) in dry DMF (5.5 mL), in an oven-dried 100 mL round-bottomed flask, was added $CsCO_3$ (1.17 g, 3.60 mmol) followed by MeI (205 µL, 3.30 mmol). The resulting mixture was heated at 60 °C overnight under an argon atmosphere. After cooling to room temperature, the reaction mixture was diluted with

water (20 mL) and then extracted with EtOAc (2 x 25 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was then purified by flash column chromatography eluting with 90:10 hexanes:EtOAc, to give **318** as a yellow oil (369 mg, 65%).

δ_H (400 MHz, $CDCl_3$): 8.08 (2 H, d, *J* 8.4, H-2), 7.40 (2 H, d, *J* 8.4, H-1), 3.79 (1 H, q, *J* 7.7, H-3), 3.60 (3 H, s, H-5), 1.46 (3 H, d, *J* 7.7, H-4).

HRMS (*m/z* -ESI): $[M-H]^-$ Found: 208.0613 $C_{10}H_{10}NO_4$ Requires: 208.0615.

2-(4 nitrophenyl)-propionaldehyde (319)[215]



An oven-dried 50 mL round-bottomed flask containing a magnetic stirring bar under an argon atmosphere was charged with a solution of **318** (1.08 g, 5.20 mmol) in CH_2Cl_2 (15 mL) and the mixture was cooled to -78 °C. DIBAL-H (1.0 M in THF, 6 mL) was then added dropwise *via* syringe over 30 min and the reaction was stirred for 24 h at -78 °C. A saturated aqueous solution of NH_4Cl, was then added at -78 °C and the reaction mixture was allowed to warm to room temperature and extracted with CH_2Cl_2 (3x 10 mL). The combined organic layers were then dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford the crude aldehyde which was purified by flash column chromatography eluting with 90:10 hexanes:EtOAc, to give **319** as a yellow oil (178 mg, 20%).

δ_H (400 MHz, $CDCl_3$): 9.70 (1 H, s, H-5), 8.22 (2 H, d, *J* 8.8, H-2), 7.37 (2 H, d, *J* 8.8, H-1), 3.77 (1 H, q, *J* 7.3, H-3), 1.50 (3 H, d, *J* 7.3 , H-4).

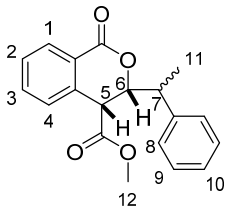
HRMS (*m/z* - ESI): $[M-H]^-$ Found: 178.0504 $C_9H_8NO_3$ Requires: 178.0508.

6.2.3 General procedure D : Synthesis of chiral diastereomeric esters and investigation into a DKR process by reacting anhydride 147 (1.0 equiv.) with the relative aldehyde (1.0 equiv.)

An oven-dried 5 mL round-bottomed flask equipped with a magnetic stirring bar was charged with the relevant aldehyde (1.0 equiv.), and catalyst **200** (5 mol%). Anhydrous

MTBE or THF (0.1 M) was added *via* syringe followed by the anhydride **147** (1.0 equiv.). The reaction mixture was stirred for the time and at the temperature indicated in Scheme 3.2 or in Table 3.1. The reaction conversion was determined by adding *p*-iodoanisole (0.5 equiv.) as an internal standard to the reaction mixture and by monitoring the disappearance of the aldehyde using ^{1}H NMR spectroscopic analysis. After the reaction was deemed complete was diluted with EtOAc (15 mL) and extracted with a 10% aqueous solution of $NaHCO_3$ (4 x 10 mL). The organic layers were dried over anhydrous $MgSO_4$ and the solvent was concentrated *in vacuo* to give the crude diastereomeric mixture of carboxylic acid products. The *dr* of the carboxylic acid products was determined by ^{1}H NMR spectroscopic analysis. The diastereomeric mixture of acids was then redissolved in dry MTBE (0.1 M) and dry MeOH (0.75 equiv.) followed by trimethylsilylsiazomethane (2.0 M solution in diethyl ether, 1.2 equiv.) were added *via* syringe. After stirring for 30 min, the solvent was removed *in vacuo* and the crude mixture of diastereomeric esters was purified by column chromatography eluting with 80:20 hexanes:EtOAc, to give a mixture of distereomers A and D – the enantiomeric excesses of which were determined by CSP-HPLC.

1-Oxo-3-(1-phenyl-ethyl)-isochroman-4-carboxylic acid methyl ester (**309a** and **311a**, Scheme 3.2)



Prepared according to procedure D, using anhydride **147** (45.3 mg, 0.280 mmol), anhydrous MTBE (0.1 M, 2.8 mL), 2-phenylpropionaldehyde **233** (33.0 µL, 0.280 mmol) and catalyst **200** (9.89 mg, 0.0140 mmol - 5 mol%). The reaction was stirred at rt for 48 h to give a mixture of carboxylic acids in 48:10:0:42 *dr* (A:B:C:D). After esterification and purification by column chromatography eluting with 80:20 hexanes:EtOAc, the mixture of diastereomers **309a** and **311a** were isolated pure as a yellow oil (39.1 mg, 42%). The enantiomeric excesses of *cis*-**309a** and *cis*-**311a** were both found to be 99%.

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA 98:2, 0.3 mL min^{-1}, RT, UV detection at 254 mm, retention times: *cis*-**309a** 69.5 min; *cis*-**311a** 118.3 min.

cis-**309a** (A):

δ_H (400 MHz, $CDCl_3$): 8.16 (1 H, m, H-1), 7.63 (1 H, app. t, *J* 7.5, H-2), 7.52 (1 H, app. t, *J* 7.5, H-3), 7.40-7.25 (3 H, m, H-9, H-10), 7.16 (2 H, d, *J* 7.4, H-8), 7.00 (1 H, d, *J* 7.7, H-4), 5.08 (1 H, dd, *J* 4.1, 9.9, H-6), 3.66 (3 H, s, H-12), 3.64 (1 H, d, *J* 4.1, H-5), 2.89-2.79 (1 H, m, H-7), 1.49 (3 H, d, *J* 6.9, H-11).

δ_C (100 MHz, $CDCl_3$): 170.3 (C=O), 163.0 (C=O), 141.73, 134.6, 133.4, 130.0, 128.9, 128.8, 128.7, 127.3, 127.6, 124.9, 83.3, 52.9, 45.6, 42.3, 19.2.

cis-**311a** (D):

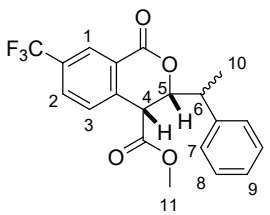
δ_H (400 MHz, $CDCl_3$): 8.17 (1 H, m, H-1), 7.44 (1 H, app. t, *J* 7.6, H-3), 7.40-7.25 (3 H, m, H-9, H-10), 7.39 (1 H, app. t, *J* 7.6, H-2), 7.25 (1 H, d, *J* 7.7, H-4), 7.18 (2 H, d, *J* 7.7, H-8), 4.70 (1 H, dd, *J* 4.1, 10.6, H-6), 3.68 (3 H, s, H-12), 3.52 (1 H, d, *J* 4.1, H-5), 3.39-3.30 (1 H, m, H-7), 1.55 (3 H, d, *J* 6.9, H-11).

δ_C (100 MHz, $CDCl_3$): 169.0 (C=O), 164.7 (C=O), 141.69, 137.0, 133.9, 130.5, 129.0, 128.9, 128.8, 127.6, 127.33, 125.1, 82.8, 52.8, 45.6, 43.3, 17.9.

ν_{max} (neat)/cm^{-1}: 2944, 1726, 1603, 1455, 1257, 1161, 1087, 1030, 799, 700.

HRMS (*m/z* - ESI): $[M+Na]^+$ Found: 333.1103 $C_{19}H_{18}O_4Na$ Requires: 333.1106.

1-Oxo-3-(1-phenyl-ethyl)-7-trifluoromethyl-isochroman-4-carboxylic acid methyl ester (**320** and **322**, Table 3.1, entry 1)



Prepared according to procedure D, using anhydride **147** (47.5 mg, 0.290 mmol), anhydrous MTBE (0.1 M, 2.9 mL), *α*-branched aldehyde **314** (58.7 mg, 0.290 mmol) and

catalyst **200** (10.2 mg, 0.0145 mmol - 5 mol%). The reaction was stirred at rt for 48 h to give a mixture of carboxylic acids in 44:7:4:45 *dr* (A:B:C:D). After esterification and purification by column chromatography eluting with 80:20 hexanes:EtOAc, the mixture of diastereomers **320** and **322** were isolated pure as a yellow oil (58.1 mg, 53%). The enantiomeric excesses of *cis*-**320** and *cis*-**322** were both found to be 99%.

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA 98:2, 0.3 mL min^{-1}, RT, UV detection at 254 mm, retention times: *cis*-**320** 57.3 min; *cis*-**322** 83.0 min.

cis-**320** (A):

δ_H (400 MHz, $CDCl_3$): 8.22 (1 H, d, *J* 8.7, H-2), 8.17 (1 H, m, H-1), 7.58-7.53 (3 H, m, H-8, H-9), 7.33 (2 H, d, *J* 8.6, H-7), 7.14 (1 H, app. t, *J* 8.7, H-3), 5.05 (1 H, dd, *J* 4.1, 8.1, H-5), 3.74 (3 H, s, H-11), 3.52 (1 H, d, *J* 4.1, H-4), 2.99-2.92 (1 H, m, H-6), 1.53 (3 H, d, *J* 6.0, H-10).

δ_c (100 MHz, $CDCl_3$): 170.4 (C=O), 162.7 (C=O), 149.2, 134.5, 134.2, 130.8 (q, J_{CF} 235), 130.4, 128.6 (q, J_{CF} 24.6), 128.4, 127.8, 125.2, 124.5, 124.0, 82.5, 52.9, 45.3, 42.9, 17.9.

δ_F (375 MHz, $CDCl_3$): -62.7

cis-**322** (D):

δ_H (400 MHz, $CDCl_3$): 8.22 (1 H, d, *J* 8.5, H-2), 8.17 (2 H, m, H-1), 7.65 (1 H, app. t, *J* 8.5, H-3), 7.58-7.53 (3 H, m, H-8, H-9), 7.47 (1 H, d, *J* 8.6, H-7), 4.67 (1 H, dd, *J* 4.1, 10.5, H-5), 3.68 (3 H, s, H-11), 3.50 (1 H, d, *J* 4.1, H-4), 2.99-2.92 (1 H, m, H-6), 1.58 (3 H, d, *J* 6.0, H-10).

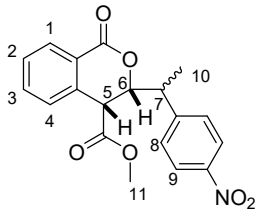
δ_c (400 MHz, $CDCl_3$): 171.7 (C=O), 168.6 (C=O), 147.2, 136.5, 134.0, 133.7, 130.6 (q, J_{CF} 234), 129.0, 128.7 (q, J_{CF} 35), 127.2, 125.0, 124.0, 124.3, 82.3, 52.8, 45.7, 43.0, 18.9.

δ_F (375 MHz, $CDCl_3$): -62.6

ν_{max} (neat)/cm^{-1}: 2946, 1729, 1603, 1457, 1324, 1248, 1161, 1073, 1000, 910, 856, 728, 660.

HRMS (*m/z* - ESI): $[M+H]^+$ Found: 379.115 $C_{20}H_{18}O_4F_3$ Requires: 379.1157.

3-[1-(4-Nitro-phenyl)-ethyl]-1-oxo-isochroman-4-carboxylic acid methyl ester) (**323** and **325**, Table 3.1, entry 2)



Prepared according to procedure D, using anhydride **147** (23.4 mg, 0.140 mmol), anhydrous THF (0.1 M, 1.4 mL), aldehyde **319** (25.4 mg, 0.140 mmol) and catalyst **200** (4.94 mg, 0.00700 mmol - 5 mol%). The reaction was stirred at rt for 48 h to give a mixture of carboxylic acids in 38:10:6:46 *dr* (A:B:C:D). After esterification and purification by column chromatography eluting with 80:20 hexanes EtOAc, the mixture of diastereomers **323** and **325** were isolated pure as a yellow oil (26.8 mg, 54%). The enantiomeric excesses of *cis*-**323** and *cis*-**325** were both found to be 99%.

CSP-HPLC analysis. Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 90:10, 0.5 mL min^{-1}, RT, UV detection at 254 mm, retention times: *cis*-**323** 54.6 min; *cis*-**325** 78.1 min.

cis-**323** (A):

δ_H (400 MHz, $CDCl_3$): 8.27 (2 H, d, *J* 8.7, H-9), 8.18 (1 H, d, *J* 8.7, H-1), 7.69-7.52 (2 H, m, H-2 and H-3), 7.48 (2 H, d, *J* 8.7, H-8), 7.18 (1 H, m, H-4), 4.68 (1 H, dd, *J* 4.4, 10.4, H-6), 3.69 (3 H, s, H-11), 3.47 (1 H, d, *J* 4.4, H-5), 3.11-2.99 (1 H, m, H-7), 1.51 (3 H, d, *J* 6.9, H-10).

δ_C (100 MHz, $CDCl_3$): 170.0 (C=O), 164.6 (C=O), 149.4, 147.1, 134.0, 130.7, 133.9, 128.8, 127.4, 125.1, 124.7, 124.2, 82.1, 52.7, 45.9, 42.4, 19.4.

cis-**325** (D):

δ_H (400 MHz, $CDCl_3$): 8.23 (2 H, d, *J* 8.7, H-9), 8.18 (1 H, d, *J* 8.7, H-1), 7.69-7.52 (2 H, m, H-2 and H-3), 7.33 (2 H, d, *J* 8.1, H-8), 7.18 (1 H, m, H-4), 5.08 (1 H, dd, *J* 4.1, 8.1, H-6), 3.75 (3 H, s, H-11), 3.50 (1 H, d, *J* 4.1, H-5), 3.56 (1 H, m, H-7), 1.54 (3 H, d, *J* 7.1, H-10).

δ_C (100 MHz, $CDCl_3$): 164.4 (C=O), 162.9 (C=O), 149.4, 147.1, 134.4, 133.9, 130.6, 128.5, 128.1, 125.1, 124.7, 123.8, 82.3, 52.8, 45.9, 42.9, 17.3.

ν_{max} (neat)/cm^{-1}: 2932, 1731, 1600, 1581, 1457, 1344, 1248, 1227, 1159, 1014, 855, 782, 755.

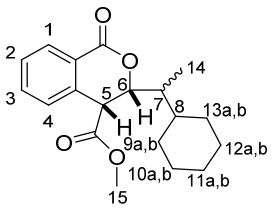
HRMS (*m/z* - ESI): $[M+H]^+$ Found: 356.1134 $C_{19}H_{18}NO_6$ Requires: 356.1136.

6.2.4 General procedure E: Synthesis of chiral diastereomeric esters, investigation into a KR process by reacting anhydride 147 (0.5 equiv.) with the relative aldehyde (1.0 equiv.) and concomitant reduction of the unreacted aldehyde to afford the corresponding alcohol (Table 3.2 and Table 3.3)

An oven dried 5 mL round-bottomed flask equipped with a magnetic stirring bar was charged with the relevant aldehyde (1.0 equiv.), and catalyst **200** or **326** (5 mol%). Anhydrous THF (0.1 M) was added *via* syringe followed by the anhydride **147** (0.5 equiv.). The reaction mixture was stirred for the time and at the temperature indicated in Table 3.2 and Table 3.3. After the reaction was deemed complete, dry MeOH (1 mL) was added *via* syringe followed by $NaBH_4$ (0.75 equiv.). The organic phase obtained was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford the crude alcohol product which was purified by flash column chromatography eluting with 70:30 hexanes:EtOAc to yield the corresponding alcohol. The basic aqueous phase was acidified by adding a 2.0 N aqueous solution of HCl dropwise which caused a fine white precipitate to form. The acidified aqueous phase was then extracted with EtOAc (4 x 10 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo* to give the crude diastereomeric mixture of the carboxylic acid products. The *dr* of the carboxylic acid products was determined by ^{1}H-NMR spectroscopic analysis. The diastereomeric mixture of acids was then redissolved in dry THF (0.1 M) and dry MeOH

(0.75 equiv.) followed by trimethylsilylsiazomethane (2.0 M solution in diethyl ether, 1.2 equiv.) were added *via* syringe. After stirring for 30 min, the solvent was removed *in vacuo* and the crude mixture of diastereomeric esters was purified by column chromatography eluting with 80:20 hexanes:EtOAc to give a mixture of distereomers A and D whose enantiomeric excesses were determined by CSP-HPLC.

3-(1-Cyclohexyl-ethyl)-1-oxo-isochroman-4-carboxylic acid methyl ester (**341**, Table 3.3, entry 1)



Prepared according to procedure E, using anhydride **147** (22.8 mg, 0.140 mmol), anhydrous THF (0.1 M, 2.8 mL), aldehyde **329** (39.5 mg, 0.280 mmol) and catalyst **326** (9.20 mg, 0.0140 mmol - 5 mol%). The reaction was stirred at rt for 48 h to give a mixture of carboxylic acids in 29:0:0:71 *dr* (A:B:C:D). After esterification and purification by column chromatography eluting with 80:20 hexanes:EtOAc, the mixture of diastereomers **341** (A and D) was isolated pure as a yellow oil (20.3 mg, 33%). The enantiomeric excesses of *cis*-**341** (A and D) were both found to be 99%.

Chiralpak IA (4.6 mm x 25 cm), hexane/IPA 98:2, 0.5 mL min^{-1}, RT, UV detection at 254 mm, retention times: *cis*-**341** (D, major diastereomer) 50.3 min; *cis*-**341** (A, minor diastereomer): 97.2 min.

cis-**341** (A):

δ_H (400 MHz, $CDCl_3$): 8.14 (1 H, d, *J* 7.6, H-1), 7.65-7.55 (1 H, m, H-2), 7.54-751 (1 H, m, H-3), 7.34 (1 H, d, *J* 7.5, H-4), 4.89 (1 H, dd, *J* 3.9, 9.3, H-6), 4.10 (1 H, d, *J* 3.9, H-5), 3.75 (3 H, s, H-15), 2.11-2.06 (1 H, m, H-7), 1.79-1.49 (5 H, m, H-9a, H-10a, H-11a, H-12a, H-13a), 1.48-1.36 (1 H, m, H-8), 1.35-0.95 (5 H, m, H-9b, H-10b, H-11b, H-12b, H-13b), 0.83 (3 H, d, *J* 6.9, H-14).

δ_C (100 MHz, $CDCl_3$): 169.2 (C=O), 164.8 (C=O), 137.0, 133.4, 130.5, 128.8, 127.0, 125.5, 80.7, 79.8, 52.4, 46.0, 40.6, 36.0, 31.4, 29.5, 26.5, 26.1, 25.6.

cis-**341** (D):

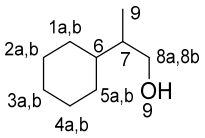
δ_H (400 MHz, $CDCl_3$): 8.17 (1 H, d, *J* 8.0, H-1), 7.65-7.55 (1 H, m, H-2),7.54-7.51 (1 H, m, H-3), 7.34 (1 H, d, *J* 7.5, H-4), 4.55 (1 H, dd, *J* 4.3, 10.5, H-6), 3.97 (1 H, d, *J* 4.3, H-5), 3.68 (3 H, s, H-15), 2.11-2.06 (1 H, m, H-7), 1.79-1.49 (5 H, m, H-9a, H-10a, H-11a, H-12a, H-13a), 1.48-1.36 (1 H, m, H-8), 1.35-0.95 (5 H, m, H-9b, H-10b, H-11b, H-12b, H-13b), 1.01 (3 H, d, *J* 6.9, H-14).

δ_C (100 MHz, $CDCl_3$): 169.2 (C=O), 164.8 (C=O), 137.0, 133.4, 130.5, 128.8, 127.0, 125.5, 80.7, 79.8, 52.4, 46.0, 40.6, 36.0, 31.4, 29.5, 26.5, 26.1, 25.6.

ν_{max} (neat)/cm^{-1}: 2922, 2852, 1727, 1709, 1603, 1455, 1377, 1265, 1165, 1087, 992, 933, 691, 744.

HRMS (*m/z* - ESI): $[M+Na]^+$ Found: 339.1572 $C_{19}H_{24}O_4Na$ Requires: 339.1577.

2-Cyclohexyl propan-1-ol (**338**, Table 3.3, entry 1)[230]



Prepared according to procedure E, using dry MeOH (1 mL) followed by $NaBH_4$ (7.94 mg, 0.210 mmol). The organic phase obtained was collected, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford the crude alcohol product which was purified by flash chromatography eluting with 80:20 hexanes:EtOAc to afford the alcohol **338** (9.35 mg, 47%, 52% *ee*).

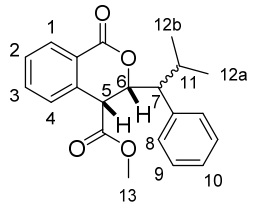
CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 98:2, 0.4 mL min^{-1}, RT, UV detection at 220 mm, retention times: 20.2 min (minor enantiomer); 31.2 min (major enantiomer).

δ_H (400 MHz, $CDCl_3$): 3.64-3.40 (2 H, m, H-8a and H-8b), 1.91-0.79 (15 H, m, H-1a, H-1b, H-2a, H-2b, H-3a, H-3b, H-4a, H-4b, H-5a, H-5b, H-6, H-7, H-9).

δ_C (100 MHz, $CDCl_3$): 66.5, 41.1, 39.6, 31.1, 29.0, 27.0, 26.9, 26.8, 13.6.

*The protic signal (H-9) is not visible in $CDCl_3$.

3-(2-Methyl-1-phenyl-propyl)-1-oxo-isochroman-4-carboxylic acid methyl ester (**342**, Table 3.3, entry 3)



Prepared according to procedure E, using anhydride **147** (25.5 mg, 0.150 mmol), anhydrous THF (0.1 M, 3.1 mL), aldehyde **330** (51.1 mg, 0.315 mmol) and catalyst **326** (10.4 mg, 0.0157 mmol - 5 mol%). The reaction was stirred at -30°C for 48 h to give a mixture of carboxylic acids in 21:0:1:78 *dr* (A:B:C:D). After esterification and purification by column chromatography eluting with 80:20 hexanes:EtOAc the mixture of diastereomers **342** (A and D) were isolated pure as a yellow oil (86.3 mg, 81%). The enantiomeric excesses of *cis*-**342** (A and D) were both found to be 99%.

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 98:2, 0.3 mL min^{-1}, RT, UV detection at 254 mm, retention times: *cis*-**342** (D, major diastereomer) 75.0 min, *cis*-**342** (A, minor diastereomer) 98.0 min.

cis-**342** (A):

δ_H (400 MHz, $CDCl_3$): 8.16 (1 H, d, *J* 7.5, H-1), 7.62-7.45 (2 H, m, H-2 and H-3) 7.41-7.29 (3 H, m, H-9 and H-10), 7.20 (1 H, d, *J* 7.9, H-4), 7.04 (2 H, d, *J* 7.7, H-8), 5.52 (1 H, dd, *J* 4.2, 11.5, H-6), 3.68 (3 H, s, H-13), 3.19 (1 H, d, *J* 4.2, H-5), 2.77- 2.59 (1 H, m, H-11), 2.58-2.46 (1 H, m, H-7), 0.98 (3 H, d, *J* 6.8, H-12a), 0.75 (3 H, d, *J* 6.8, H-12b).

δ_C(100 MHz, $CDCl_3$): 170.9 (C=O), 163.6 (C=O), 137.4, 134.5, 134.0, 130.8, 129.2, 129.1, 128.8, 128.6, 127.3, 125.0, 80.0, 54.2 52.9, 45.8, 28.1, 21.6, 17.5.

cis-**342** (D):

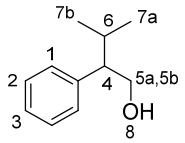
δ_H (400 MHz, $CDCl_3$): 8.19 (1 H, d, *J* 7.5, H-1), 7.62-7.45 (2 H, m, H-2 and H-3) 7.41-7.29 (3 H, m, H-9 and H-10), 7.12 (1 H, d, *J* 7.9, H-4), 6.96 (2 H, d, *J* 7.7, H-8), 5.04 (1 H, dd, *J* 4.7, 11.2, H-6) 3.62 (3 H, s, H-13), 3.16 (1 H, d, *J* 4.7, H-5), 2.77- 2.59 (1 H, m, H-11), 2.44-2.27 (1 H, m, H-7), 0.90 (3 H, d, *J* 6.8, H-12a), 0.84 (3 H, d, *J* 6.8, H-12b).

δ_C(100 MHz, $CDCl_3$): 169.7 (C=O), 164.8 (C=O), 137.2, 136.6, 133.7, 130.7, 128.9, 128.2 (Cx2), 127.4, 127.3, 125.3, 78.8, 53.0, 52.2, 45.9, 27.1, 21.4, 16.5.

ν_{max} (neat)/cm^{-1}: 2933, 1728, 1704, 1494, 1365, 1314, 1158, 1134, 854, 782, 754, 723, 701.

HRMS (*m/z* - ESI): $[M+Na]^+$ Found: 361.1413 $C_{21}H_{22}O_4Na$ Requires: 361.1416.

3-Methyl-2-phenyl-butan-1-ol (**339**, Table 3.3 entry 3)[231]



Prepared according to procedure E, using dry MeOH (1 mL) followed by $NaBH_4$ (8.92, 0.236 mmol). The organic phases obtained was collected, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford the crude alcohol product which was purified by flash column chromatography eluting with 70:30 hexanes:EtOAc to obtain the corresponding alcohol **339** as a colourless (24.3 mg, 48%, 66% *ee*).

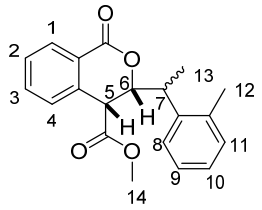
CSP-HPLC analysis. Chiralpak ADH (4.6 mm x 25 cm), hexane/IPA: 98:2, 1.0 mL min^{-1}, RT, UV detection at 254 mm, retention times: 11.8 min (major enantiomer) and 13.3 min (minor enantiomer).

δ_H (400 MHz, $CDCl_3$): 7.33-7.13 (5 H, m, H-1, H-2, H-3), 3.94-3.79 (2 H, m, H-5a and H-5b), 2.52-2.46 (1 H, m, H-4), 1.96-1.81 (1 H, m, H-6), 0.95 (3 H, d, *J* 6.7, H-7a), 0.72 (3 H, d, *J* 6.7, H-7b).

δ_C (100 MHz, $CDCl_3$): 141.7 (q), 128.7, 128.5, 126.7, 65.2, 55.8, 30.1, 21.0.

*The protic signal (H-8) is not visible in $CDCl_3$.

1-Oxo-3-(1-o-tolyl-ethyl)-isochroman-4-carboxylic acid methyl ester (**343**, Table 3.3, entry 5)



Prepared according to procedure E, using anhydride **147** (16.8 mg, 0.100 mmol), anhydrous THF (0.1 M, 2.0 mL), aldehyde **331** (30.8 mg, 0.200 mmol) and catalyst **326** (6.60 mg, 0.0100 mmol - 5 mol%). The reaction was stirred at -60 °C for 48 h to give a mixture of carboxylic acids in 5:0:0:95 *dr* (A:B:C:D). After esterification and purification by column chromatography eluting with 80:20 hexanes:EtOAc, the mixture of diastereomers **343** (A and D) were isolated pure as a yellow oil (35.7 mg, 55%). The enantiomeric excesses of *cis*-**343** (A and D) were both found to be 99%.

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 98:2, 0.4 mL min^{-1}, RT, UV detection at 254 mm, retention times: *cis*-**343** (D, major diastereomer) 80 min; *cis*-**343** (A, minor diastereomer) 45.3 (major enantiomer) and 55.5 (minor enantiomer).

Only the major diastereomer assigned for ^{13}C NMR.

cis-**343** (A):

δ_H (400 MHz, $CDCl_3$): 8.19 (1 H, d, *J* 7.5, H-1), 7.61-7.46 (3 H, m, H-2, H-3, H-4), 7.27-7.08 (4 H, m, H-8, H-9, H-10, and H-11) 5.20 (1 H, dd, *J* 4.1, 10.4, H-6) 3.74 (1 H, d, *J* 4.1, H-5), 3.62 (3 H, s, H-14), 3.35-3.16 (1 H, m, H-7) 2.36 (3 H, s, H-12), 1.45 (3 H, d, *J* 6.6, H-13).

cis-**343** (D):

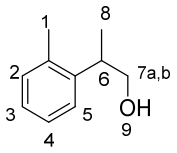
δ_H (400 MHz, $CDCl_3$): 8.19 (1 H, d, *J* 7.5, H-1), 7.61-7.46 (3 H, m, H-2, H-3, H-4), 7.27-7.08 (4 H, m, H-8, H-9, H-10, and H-11) 4.87 (1 H, dd, *J* 4.4, 10.5, H-6), 3.71 (1 H, d, *J* 4.4, H-5), 3.63 (3 H, s, H-14), 3.17-3.11 (1 H, m, H-7) 2.36 (3 H, s, H-12), 1.47 (3 H, d, *J* 6.6, H-13).

δ_C (100 MHz, $CDCl_3$): 170.0 (C=O), 164.7 (C=O), 140.3, 137.0, 135.8, 135.2, 133.5, 130.9, 130.6, 128.8, 127.3, 126.6, 126.5, 125.1, 82.7, 52.6, 45.6, 29.5, 19.6, 19.2.

ν_{max} (neat)/cm^{-1}: 2927, 1733, 1603, 1456, 1374, 1120, 1083, 1008, 758, 727, 699.

HRMS (*m/z* - ESI): $[M+Na]^+$ Found: 367.1249 $C_{20}H_{20}O_4Na$ Requires: 347.1259.

2-(2-Methyl-phenyl)-propan-1-ol (**340**, Table 3.3, entry 5)[232]



Prepared according to procedure E, using dry MeOH (1 mL) followed by $NaBH_4$ (5.67 mg, 0.150 mmol). The organic phase obtained was collected, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford the crude alcohol product which was purified by flash column chromatography eluting with 70:30 hexanes/EtOAc, to furnish the alcohol **340** as a colourless oil (7.60 mg, 51%, 60% *ee*).

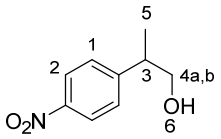
CSP-HPLC analysis. Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 90:10, 0.5 mL min^{-1}, RT, UV detection at 254 mm, retention times: 54.6 min (major diastereomer) and 78.1 (minor diastereomer).

δ_H (400 MHz, $CDCl_3$): 7.23-7.10 (4 H, m, H-2, H-3, H-4, H-5), 3.76-3.61 (2 H, m, H-7a and H-7b), 3.30-3.19 (1 H, m, H-6), 2.38 (3 H, s, H-1), 1.26 (3 H, d, *J* 6.9, H-8).

δ_C (100 MHz, $CDCl_3$): 141.7, 136.2, 130.4, 126.2, 126.1, 125.4, 67.9, 37.2, 19.5, 17.4.

*The protic signal (H-9) is not visible in $CDCl_3$.

2-(4-Nitro-phenyl)-propan-1-ol (**327**, Table 3.2 entry 2)[232]



Prepared according to procedure E, using dry MeOH (1 mL) followed by $NaBH_4$ (6.96 mg, 0.184 mmol). The organic phase obtained was collected, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford the crude alcohol product which was purified by flash column chromatography eluting with 70:30 hexanes:EtOAc, to furnish **327** as a colourless oil (3.50 mg, 39%, 45% *ee*).

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 95:5, 0.3 mL min^{-1}, RT, UV detection at 254 mm, retention times: 73.9 min (major enantiomer); 78.2 min, (minor enantiomer).

δ_H (400 MHz, $CDCl_3$): 7.52 (2 H, d, *J* 8.7, H-2), 7.38 (2 H, d, *J* 8.7, H-1), 5.01-4.95 (2 H, m, H-4a,b), 3.09-3.03 (1 H, m, H-3), 0.93 (3 H, d, *J* 6.6, H-5).

δ_C (100 MHz, $CDCl_3$): 152.2, 146.9, 128.6, 123.9, 68.1, 42.6, 25.8, 17.6.

*The protic signal (H-6) is not visible in $CDCl_3$.

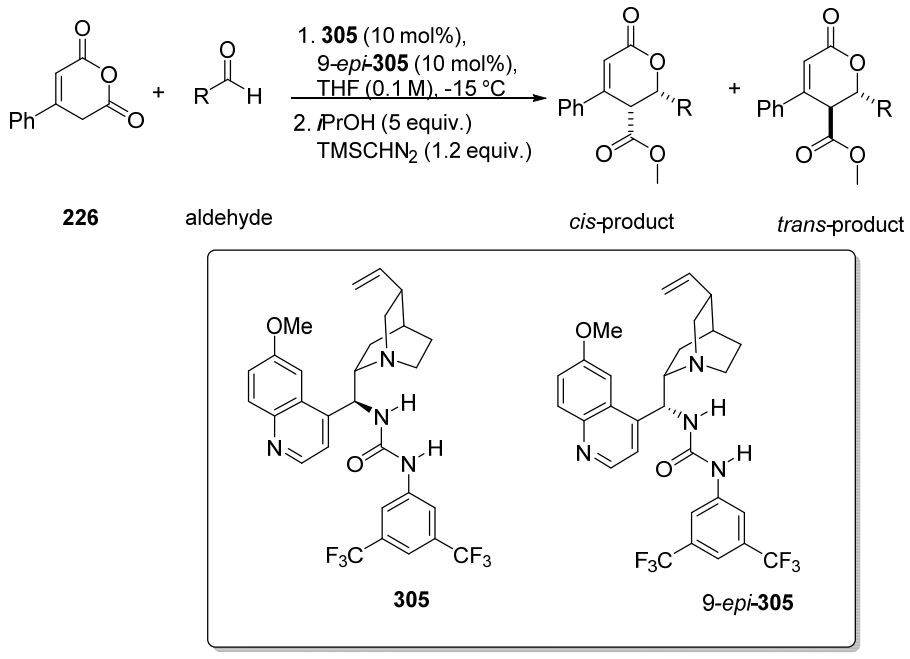
6.4 Experimental procedure and data for Chapter 4

6.4.1 General procedure F: racemic synthesis of dihydroisocoumarins and *γ*-butyrolactones (Tables 4.1-4.7)

An oven-dried 10 mL round-bottomed flask containing a magnetic stirring bar under an argon atmosphere was charged with the relevant anhydride (1 equiv.) and anhydrous THF (2.5 mL, 0.1 M). The relevant aldehyde (1 equiv.) followed by *N*,*N*-diisopropylethylamine (8.6 µL, 0.0492 mmol - 20 mol%) were then added *via* syringe and the resulting mixture was allowed to stir for 20 h at room temperature. To the

corresponding solution of carboxylic acids in THF (2.5 mL, 0.1 M), were added *via* syringe anhydrous MeOH (750 µL, 18.5 mmol), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 150 µL, 0.300 mmol) and the reaction was allowed to stir for 30 min at room temperature. The solvent was then removed *in vacuo* and the crude mixture of diastereomeric esters was purified by flash column chromatography to afford both diastereomers.

6.4.2 General procedure G: racemic synthesis of 442, 445 and 447



An oven-dried 10 mL round-bottomed flask containing a magnetic stirring bar under an argon atmosphere was charged with phenyl glutaconic anhydride (**226**, 46.3 mg, 0.246 mmol) and anhydrous THF (2.5 mL, 0.1 M). The relevant aldehyde (1 equiv.) was then added to the reaction followed by equal amounts of catalyst **305** (14.2 mg, 0.0246 mmol -10 mol%) and its pseudoenantiomer catalyst *epi*-**305** (14.2 mg, 0.0246 mmol - 10 mol%) and the resulting mixture was allowed to stir for 20 h at room temperature. The corresponding solution of carboxylic acids in dry THF (2.5 mL, 0.1 M) was then cooled to -15 °C and anhydrous *i*PrOH (94 µL, 1.23 mmol), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 150 µL, 0.300 mmol) were added *via* syringe. The reaction was allowed to stir for 20 min at -15 °C, after which time the solvent was removed *in vacuo*. The resultant crude mixture of diastereomeric esters was then purified by flash column chromatography to furnish both diastereomers.

6.4.3 General procedure H: enantioselective preparation of dihydroisocoumarins and γ-butyrolactones (Tables 4.1-4.7)

An oven-dried 10 mL round-bottomed flask containing a magnetic stirring bar under an argon atmosphere was charged with the relevant anhydride (1.0 equiv.), catalyst **326** (8.13 mg, 0.0123 mmol - 5 mol%) and anhydrous THF (0.1 M). The resulting mixture was cooled to -15 °C and the relevant aldehyde (1 equiv.) was added *via* syringe. The reaction was allowed to stir at -15 °C and for a time indicated in the relative Table. The yield and diastereomeric ratio of the carboxylic acids were determined by ^{1}H NMR spectroscopic analysis using *p*-iodoanisole (0.5 equiv.) as an internal standard. The reaction was then diluted with EtOAc (10 mL) and extracted with a 10% aqueous solution of $NaHCO_3$ (15 mL). The combined aqueous phases were acidified with an aqueous solution of HCl (2.0 N, 5 mL) and the mixture was then extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to furnish the diastereomeric mixture of carboxylic acids. To a solution of the carboxylic acid products in dry THF (0.1 M) were added *via* syringe anhydrous MeOH (750 μL, 18.5 mmol) followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 150 μL, 0.300 mmol) and the reaction was allowed to stir for 20 min. The solvent was then evaporated *in vacuo* and the crude mixture of diastereomeric esters was purified by flash column chromatography, to isolated both diastereomers – the enantiomeric excesses of which were determined by CSP-HPLC.

6.4.4 General procedure I: enantioselective preparation of 442, 445 and 447 (Tables 4.8 and 4.10)

An oven-dried 10 mL round-bottomed flask containing a magnetic stirring bar under an argon atmosphere was charged with phenyl glutaconic anhydride (**226**, 46.3 mg, 0.246 mmol), catalyst **326** (8.13 mg, 0.0123 mmol - 5 mol%) and anhydrous THF (0.1 M). The resulting mixture was cooled to -15 °C and the relevant aldehyde (1 equiv.) was added *via* syringe. The reaction was allowed to stir at -15 °C and for a time indicated in the relative Table. The yield and diastereomeric ratio of the carboxylic acids were determined by ^{1}H NMR spectroscopic analysis using *p*-iodoanisole (0.5 equiv.) as an internal standard. The reaction was then diluted with EtOAc (10 mL) and extracted with a 10% aqueous solution of $NaHCO_3$ (15 mL). The combined aqueous phases were acidified with an aqueous solution of HCl (2.0 N, 5 mL) and the mixture was then extracted with EtOAc

(3 x 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to furnish the diastereomeric mixture of carboxylic acids. To a solution of the corresponding carboxylic acids in dry THF (0.1 M) cooled to -15 °C, were added *via* syringe anhydrous *i*PrOH (94 µL, 1.23 mmol), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 150 µL, 0.300 mmol) and the reaction was allowed to stir for 20 minutes at -15 °C. The solvent was then evaporated under reduced pressure and the crude mixture of diastereomeric esters was purified by flash column chromatography to furnish both diastereomers. The enantiomeric excesses of the products were determined by CSP-HPLC using the conditions indicated for each case.

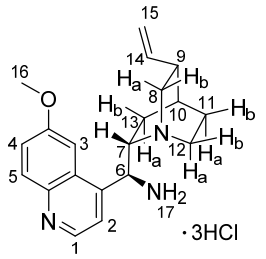
6.4.5 General procedure J: racemic synthesis of *cis*-453 and *trans*-453

An oven-dried 10 mL round-bottomed flask containing a magnetic stirring bar under an argon atmosphere was charged with homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol) and anhydrous THF (2.5 mL, 0.1 M). Isovaleraldehyde (27.0 µL, 0.246 mmol) followed by *N*,*N*-diisopropylethylamine (8.6 µL, 0.0495 mmol - 20 mol%) were added *via* syringe and the reaction was allowed to stir for 18 h at room temperature. The reaction was then diluted with EtOAc (10 mL) and extracted with a 10% aqueous solution of $NaHCO_3$ (15 mL). The combined aqueous phases were acidified with an aqueous solution of HCl (2.0 N, 5 mL) and the mixture was then extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to furnish the diastereomeric mixture of carboxylic acids. To a solution of the corresponding carboxylic acids in dry CH_2Cl_2 (1 mL), dry DMF (5 µL), followed by oxalyl chloride (2.0 M solution in CH_2Cl_2, 187 µL, 0.300 mmol) were added *via* syringe at 0 °C. The reaction mixture was allowed to stir for 1 h at room temperature. Benzylamine (80.6 µL, 0.738 mmol) was then added *via* syringe at 0 °C and the reaction mixture was stirred for 1 h at room temperature. The resulting suspension was then diluted with water (10 mL) and extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude diastereomeric mixture of carboxamide lactones was purified by flash column chromatography to furnish *cis*-**453** and *trans*-**453** as single diastereomers.

6.4.6 General procedure K: enantioselective synthesis of *cis*-453 and *trans*-453 (Tables 4.11, entry 5)

An oven-dried 10 mL round-bottomed flask containing a magnetic stirring bar under an argon atmosphere was charged with homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol), catalyst **326** (8.13 mg, 0.0123 mmol, 5 mol%) and anhydrous THF (0.1 M). The resulting mixture was cooled to -15 °C and freshly distilled isovaleraldehyde (26.9 µL, 0.246 mmol) was added *via* syringe. The reaction was allowed to stir for 18 h at -15 °C. The yield and diastereomeric ratio of the carboxylic acids were determined by ^{1}H NMR spectroscopic analysis using *p*-iodoanisole (0.5 equiv.) as an internal standard. The reaction was then diluted with EtOAc (10 mL) and extracted with a 10% aqueous solution of $NaHCO_3$ (15 mL). The combined aqueous phases were acidified with an aqueous solution of HCl (2.0 N, 5 mL) and the mixture was then extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to furnish the diastereomeric mixture of carboxylic acids. The carboxylic acid products were then dissolved in dry CH_2Cl_2 (1 mL) and DMF (5 µL), followed by oxalyl chloride (2.0 M solution in CH_2Cl_2, 187 µL, 0.300 mmol) were added *via* syringe at 0 °C. The reaction mixture was allowed to stir for 1 h at room temperature. Benzylamine (80.6 µL, 0.738 mmol) was then added *via* syringe at 0 °C and the reaction mixture was stirred for 1 h at room temperature. The resulting suspension was then diluted with water (10 mL) and extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude diastereomeric mixture of carboxamide lactones was then purified by flash column chromatography to furnish *cis*-**453** and *trans*-**453** as single diastereomers. The enantiomeric excesses of the products were determined by CSP-HPLC.

(*S*)-(6-Methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanamine·3HCl (354a)[233]

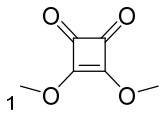


A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with quinine (**79**, 5.00 g, 15.4 mmol), triphenylphosphine (4.85 g, 2.42 mmol) and dry THF (70 mL). Diisopropyl azodicarboxylate (DIAD) (3.6 mL, 18.5 mmol) was added *via* syringe. at 0 °C under an argon atmosphere and the reaction mixture was stirred at 0 °C for 30 min. A solution of diphenylphosphoryl azide (DPPA, 4.0 mL, 18.5 mmol) in dry THF (32 mL) was then added dropwise. The reaction mixture was allowed to stir for 12 h at room temperature and then heated at 50 °C for an additional 2 h. After cooling the reaction mixture to room temperature, triphenylphosphine (5.30 g, 20.0 mmol) was added portionwise. The reaction was then heated at 50 °C for 2 h after which time, the resultant mixture was cooled to room temperature, diluted with water (5 mL) and allowed to stir for 4 h. The organic volatiles were removed under reduced pressure and the residue was dissolved in an aqueous solution of HCl (2.0 N, 20 mL). The aqueous layer was washed with CH_2Cl_2 (3 x 20 mL) and concentrated *in vacuo* to afford **354a** as a yellow solid (5.53 g, 83%). M.p. 218-222 °C, (lit.[233] m.p. 220-222 °C). $[\alpha]_D^{20}$ = +19.0 (*c* = 0.75, MeOH), $[\alpha]_D^{20}$ = +22.1 (*c* = 0.75, MeOH).[235]

δ_H (400 MHz, D_2O):* 9.03 (1 H, d, *J* 5.8, H-1), 8.27 (1 H, d, *J* 9.4, H-5), 8.12 (1 H, d, *J* 5.8, H-2), 7.96 (1 H, dd, *J* 2.4, 9.4 H-4), 7.83 (1 H, bs, H-3), 5.90 (1 H, ddd, *J* 6.8, 10.5, 17.2, H-14), 5.53 (1 H, d, *J* 10.6, H-6), 5.32-5.18 (2 H, m, H-15), 4.34-4.22 (1 H, m, H-7), 4.11 (3 H, s, H-16), 4.04-3.92 (1 H, m, H-12a), 3.85 (1 H, dd, *J* 10.6, 13.3, H-8b), 3.59-3.45 (2 H, m, H-8a, H-12b), 3.02-2.93 (1 H, m, H-9), 2.17-2.00 (3 H, m, H-10, H-11a and H-11b), 1.96-1.84 (1 H, m, H-13b), 1.18 (1 H, dd, *J* 7.2, 14.2, H-13a).

* The protic signal (H-17) is not visible in D_2O.

3,4-Dimethoxycyclobut-3-ene-1,2-dione (**357**)[234]

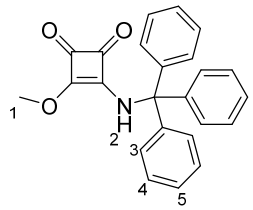


A 50 mL round-bottomed flask containing a magnetic stirring bar under an argon atmosphere was charged with squaric acid (**355**, 2.00 g, 17.5 mmol), dry MeOH (20 mL),

followed by trimethyl orthoformate (**356**, 5.7 mL, 52.6 mmol) and TFA (269 μL, 3.50 mmol). The flask was fitted with a condenser and the reaction mixture was heated at reflux temperature for 48 h and then cooled to room temperature. The solvent was removed *in vacuo* to afford a crude residue which was purified by flash column chromatography eluting with 70:30 hexanes:EtOAc, to furnish **357** as white solid (1.90 g, 76%). M.p. 51-53 °C (lit.[234] m.p. 52-54 °C).

δ_H (400 MHz, $CDCl_3$): 4.38 (6 H, s, H-1).

3-Methoxy-4-(tritylamino)cyclobut-3-ene-1,2-dione (**359**)



To a 25 mL round-bottomed flask containing a magnetic stirring bar under an argon atmosphere was added a solution of **357** (1.60 g, 11.4 mmol) in dry MeOH (11.4 mL) followed by tritylamine (**358**, 2.90 g, 11.4 mmol). The solution was allowed to stir at room temperature for 48 h. The precipitate formed was then filtered, washed with MeOH and dried to afford **359** as an off white solid (2.44 g, 58%). M.p. 193-196°C.

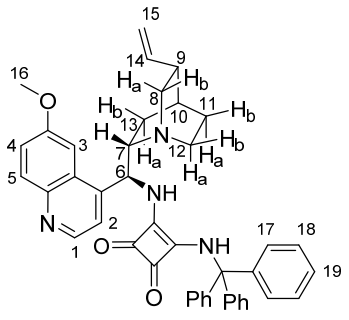
δ_H (400 MHz, $CDCl_3$): 7.39-7.30 (9 H, m, H-4 and H-5), 7.16-7.09 (6 H, m, H-3), 6.81 (1 H, bs, H-2), 3.79 (3 H, bs, H-1).

δ_C (100 MHz, $CDCl_3$): 189.3 (C=O), 184.5 (C=O), 178.2, 172.3, 143.7 (q x 3), 128.7, 128.3, 127.9, 72.9, 59.8.

ν_{max} (neat)/cm^{-1}: 3379, 3287, 1802, 1701, 1594, 1490, 1441, 1365, 1058, 1090, 956, 831, 769, 699.

HRMS (*m/z* - APCI): $[M-H]^-$ Found: 368.1296 $C_{24}H_{18}NO_3$ Requires: 3681292.

3-(((*S*)-(6-Methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-4-(tritylamino)cyclobut-3-ene-1,2-dione (326)[235]

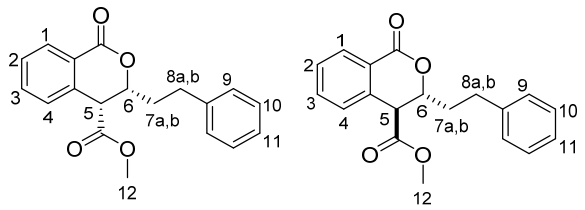


A 100 mL oven dried round-bottomed flask was charged with **354a** (2.00 g, 6.40 mmol). CH_2Cl_2 (15 mL) followed by freshly distilled triethylamine (3.5 mL, 25.2 mmol) were added *via* syringe and the resultant mixture was stirred at room temperature for 1 h. Water (20 mL) was then added and the organic phases separated and dried over anhydrous $MgSO_4$. The volatiles were removed *in vacuo* and the residue was dissolved in MeOH (12.7 mL) and transferred to a 50 mL round-bottomed flask. Compound **359** (2.36 g, 6.40 mmol) was added in one portion and the reaction mixture was allowed to stir at room temperature for 48 h under an argon atmosphere. The solvent was removed under reduced pressure and then resulting solid residue was purified by flash column chromatography (hexanes:EtOAc:MeOH: NEt_3 7:1.5:1:0.5) to give **326** as a white solid (3.85 g, 91%). M.p. 156-158°C, (lit.[235] m.p. 220-222 °C), $[\alpha]_D^{20}$ = +41.7 (*c* = 0.10, $CHCl_3$), $[\alpha]_D^{20}$ = +41.8 (*c* = 0.10, $CHCl_3$).[235]

δ_H (400 MHz, $CDCl_3$): 8.61 (1 H, d, *J* 4.5, H-1), 7.99 (1 H, d, *J* 9.1, H-5), 7.56-7.46 (1 H, bs, H-3), 7.38 (1 H, dd, *J* 2.3, 9.2, H-4), 7.20-7.09 (9 H, m, H-20 and H-21), 7.07-6.91 (6 H, m, H-19), 6.55 (1 H, bs, H-2), 6.39 (1 H, bs, N-H), 5.91-5.71 (2 H, m, H-6 and H-14), 5.06-4.96 (2 H, m, H-15), 3.90 (3 H, s, H-16), 3.69 (1 H, bs, N-H), 3.34-3.12 (2 H, m, H-8b and H-12a), 2.67-2.46 (3 H, m, H-7, H-8a and H-12b), 2.31-2.21 (1 H, m, H-9), 1.70-1.58 (1 H, m, H-10), 1.55-1.40 (3 H, m, H-11a, H-11b and H-13b), 0.74-0.57 (1 H, m, H-13a).

HRMS (*m/z* - APCI): $[M-H]^-$ Found: 661.3180 $C_{43}H_{40}N_4O_3$ Requires: 661.3173.

Methyl-1-oxo-3-((*E*)-styryl)isochromane-4-carboxylate (*cis*-**204**, *trans*-**204**, Table 4.2, entry 1)[150]



Prepared according to general procedure H, using freshly distilled hydrocinnamaldehyde (**202**, 32.0 μL, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 33 h to give a diastereomeric mixture of carboxylic acids in a 71:29 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 80:20 hexanes:EtOAc, *cis*-**204** and *trans*-**204** were isolated combined as a pale yellow oil (74.0 mg, 99%). TLC (hexanes/EtOAc, 8:2 *v/v*): $R_f = 0.34$. The enantiomeric excesses of *cis*-**204** and *trans*-**204** were found to be 90% and 91% respectively.

CSP-HPLC analysis. Chiralcel OJ-H (4.6 mm x 25 cm), hexane/IPA: 70/30, 0.3 mL min^{-1}, RT, UV detection at 254 nm, retention times: *cis*-**204** 70.4 min (major enantiomer) and 105.9 min (minor enantiomer); *trans*-**204** 60.6 min (major enantiomer) and 79.2 min (minor enantiomer).

cis-**204**:

δ_H (400 MHz, $CDCl_3$): 8.15 (1 H, d, *J* 7.9, H-1), 7.56 (1 H, app. t, *J* 7.9, H-2), 7.48 (1 H, app. t, *J* 7.9, H-3), 7.32-7.24 (2 H, m, H-9), 7.25-7.14 (4 H, m, H-4, H-10 and H-11), 4.60-4.52 (1 H, m, H-6), 3.83 (1 H, d, *J* 3.2, H-5), 3.67 (3 H, s, H-12), 3.05-2.90 (1 H, m, H-8a), 2.90-2.83 (1 H, m, H-8b), 2.31-2.18 (1 H, m, H-7a), 2.14-2.02 (1 H, m, H-7b).

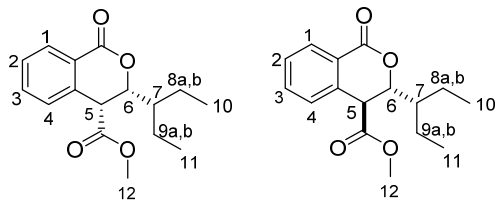
trans-**204**:

δ_H (400 MHz, $CDCl_3$): 8.15 (1 H, d, *J* 7.7, H-1), 7.57 (1 H, app. t, *J* 7.7, H-2), 7.47 (1 H, app. t, *J* 7.7, H-3), 7.32-7.24 (3 H, m, H-9 and H-11), 7.25-7.14 (3 H, m, H-4 and H-10), 4.90-4.82 (1 H, m, H-6),

3.92 (1 H, d, *J* 6.8, H-5), 3.76 (3 H, s, H-12), 3.05-2.90 (1 H, m, H-8a), 2.83-2.75 (1 H, m, H-8b), 2.15-2.01 (1 H, m, H-7a), 1.99-1.84 (1 H, m, H-7b).

HRMS (*m/z* - APCI): $[M+H]^+$ Found: 311.1284 $C_{19}H_{19}O_4$ Requires: 311.1277.

Methyl-1-oxo-3-(pentan-3-yl)isochromane-4-carboxylate (*cis*-**360**, *trans*-**360**, Table 4.3, entry 1)



Prepared according to general procedure H, using freshly distilled 2-ethylbutyraldehyde (**403**, 30.3 µL, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 6 days to give a diastereomeric mixture of carboxylic acids in a 90:10 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 95:5 hexanes:EtOAc, *cis*-**360** and *trans*-**360** were isolated combined as a white solid (61.2 mg, 90%). M.p. 45-47 °C, TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.64, $[\alpha]_D^{20}$ = -3.9 (*c* = 0.04, $CHCl_3$).* The enantiomeric excesses of *cis*-**360** and *trans*-**360** were both found to be 99%.

CSP-HPLC analysis. ACQUITY UPC^2, Trefoil AMY1, 2.5µm (3.0 x 150mm). ABPR: 1500 (psi). A (CO_2) = 97%/B (Ethanol/ACN/IPA 1:1:1, *v:v:v*) = 3%, 1.2 mL min^{-1}, 30 °C, UV detection at 254 nm, retention times: *cis*-**360** 2.05 min; *trans*-**360** 2.02 min.

cis-**360**:

δ_H (400 MHz, $CDCl_3$): 8.16 (1 H, d, *J* 7.7, H-1), 7.58 (1 H, app. t, *J* 7.7, H-2), 7.50 (1 H, app. t, *J* 7.7, H-3), 7.34 (1 H, d, *J* 7.7, H-4), 4.45 (1 H, dd, *J* 2.9, 9.8, H-6), 4.01 (1 H, d, *J* 2.9, H-5), 3.68 (3 H, s, H-12), 1.90-1.77 (3 H, m, H-7, H-8a and H-9a), 1.70-1.59 (1 H, m, H-8b), 1.55-1.42 (1 H, m, H-9b), 0.94-0.88 (6 H, m, H-10 and H-11).

δ_C (100 MHz, $CDCl_3$): 169.5 (C=O), 165.0 (C=O), 137.2, 133.6, 130.7, 129.0, 127.3, 125.6, 80.6, 52.6, 46.1, 41.7, 20.0, 19.7, 9.8, 9.6.

trans-**360**:

δ_H (400 MHz, $CDCl_3$): 8.14 (1 H, d, *J* 7.6, H-1), 7.61 (1 H, app. t, *J* 7.6, H-2), 7.50 (1 H, app. t, *J* 7.6, H-3), 7.23 (1 H, d, *J* 7.6, H-4), 4.90-4.84 (1 H, m, H-6), 4.14 (1 H, d, *J* 6.7, H-5), 3.80 (3 H, s, H-12), 1.90-1.77 (3 H, m, H-7, H-8a and H-9a), 1.70-1.59 (1 H, m, H-8b), 1.55-1.42 (1 H, m, H-9b), 0.94-0.88 (6 H, m, H-10 and H-11).

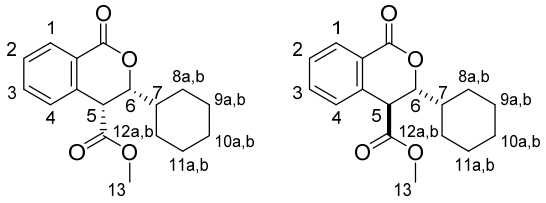
δ_C (100 MHz, $CDCl_3$): 170.9 (C=O), 164.2 (C=O), 136.3, 134.0, 130.4, 128.6, 127.2, 124.8, 80.7, 52.7, 46.2, 43.2, 21.9, 20.9, 11.2, 10.8.

ν_{max} (neat)/cm^{-1}: 2963, 2878, 1724, 1604, 1458, 1264,1226, 1158, 1110, 1085, 997, 717, 691.

HRMS (*m/z* -ESI): $[M+Na]^+$ Found: 299.1279 $C_{16}H_{20}O_4Na$ Requires: 299.1259.

*$[\alpha]_D^{20}$ refers to a mixture of *cis*-**360**:*trans*-**360** in a 90:10 ratio

Methyl-3-cyclohexyl-1-oxoisochroman-4-carboxylate (*cis*-**203***, trans*-**203**, Table 4.3, entry 2)[151]



Prepared according to general procedure H using freshly distilled cyclohexanecarboxyaldehyde (**201**, 29.8 μL, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 24 h to give a diastereomeric mixture of carboxylic acids in a 80:20 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 90:10 hexanes:EtOAc, *cis*-**203** and *trans*-**203** were isolated combined as a pale yellow oil (67.4 mg, 95%). The enantiomeric excesses of *cis*-**203** and *trans*-**203** were both found to be 98%.

CSP-HPLC analysis. Chiralcel ODH (4.6 mm x 25 cm), hexane/IPA: 60/40, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: *cis*-**203** 62.3 min (minor enantiomer) and 65.1 min (major enantiomer); *trans*-**203** 51.8 min (major enantiomer) and 62.3 min (minor enantiomer).

cis-**203**:

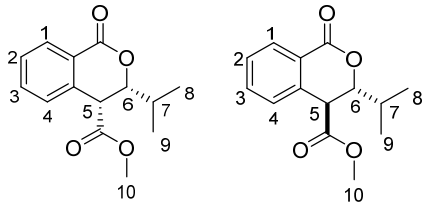
δ_H (400 MHz, $CDCl_3$): 8.16 (1 H, d, *J* 7.6, H-1), 7.58 (1 H, app. t, *J* 7.6, H-2), 7.50 (1 H, app. t, *J* 7.6, H-3), 7.33 (1 H, d, *J* 7.6, H-4), 4.26 (1 H, dd, *J* 3.0, 9.9, H-6), 4.03 (1 H, d, *J* 3.0, H-5), 3.69 (3 H, s, H-13), 2.41-2.23 (1 H, m, H-7), 2.03-1.08 (8 H, m, H-8a,b, H-9a,b, H-11a,b and H-12a,b), 1.08-0.95 (2 H, m, H-10a and H-10b).

trans-**203**:

δ_H (400 MHz, $CDCl_3$): 8.13 (1 H, d, *J* 7.9, H-1), 7.58 (1 H, app. t, *J* 7.9, H-2), 7.46 (1 H, app. t, *J* 7.9, H-3), 7.22 (1 H, d, *J* 7.9, H-4), 4.66 (1 H, m, H-6), 4.06 (1 H, d, *J* 5.7, H-5), 3.77 (3 H, s, H-13), 1.97-1.88 (1 H, m, H-7), 1.87-1.08 (10 H, m, H-8a,b, H-9a,b and H-10a,b, H-11a,b and H-12a,b).

HRMS (*m/z* -APCI): $[M-H]^-$ Found: 287.1277 $C_{17}H_{19}O_4$ Requires: 287.1288.

Methyl-3-isopropyl-1-oxoisochromane-4-carboxylate (*cis*-**361**, *trans*-**361**, Table 4.3, entry 3)



Prepared according to general procedure H, using freshly distilled isobutyraldehyde (22.4 µL, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 18 h to give a diastereomeric mixture of carboxylic acids in a 84:16 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 85:15 hexanes:EtAOc, *cis*-**361** and *trans*-**361** were isolated combined as a white

solid (54.9 mg, 90%). M.p. 69-72 °C, TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.26, $[\alpha]_D^{20}$ = -5.1 (*c* = 0.05, $CHCl_3$).* The enantiomeric excesses of *cis*-**361** and *trans*-**361** were both found to be 99%.

CSP-HPLC analysis. Chiralcel ODH (4.6 mm x 25 cm), hexane/IPA: 85/15, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: *cis*-**361** 21.8 min; *trans*-**361** 15.2 min.

cis-**361**:

δ_H (400 MHz, $CDCl_3$): 8.16 (1 H, d, *J* 7.5, H-1), 7.58 (1 H, app. t, *J* 7.5, H-2), 7.50 (1 H, app. t, *J* 7.5, H-3), 7.33 (1 H, d, *J* 7.5, H-4), 4.17 (1 H, dd, *J* 3.0, 9.9, H-6) ,4.03 (1 H, d, *J* 3.0, H-5), 3.67 (3 H, s, H-10), 2.17-2.01 (1 H, m, H-7), 1.20 (3 H, d, *J* 6.8, H-8), 1.12 (3 H, d, *J* 6.8, H-9).

δ_C (100 MHz, $CDCl_3$): 169.4 (C=O), 164.9 (C=O), 137.1, 133.7, 130.7, 129.0, 127.3, 125.6, 84.4, 52.6, 46.2, 31.1, 18.5, 19.4.

trans-**361**:

δ_H (400 MHz, $CDCl_3$): 8.14 (1 H, d, *J* 7.8, H-1), 7.60 (1 H, app. t, *J* 7.8, H-2), 7.48 (1 H, app. t, *J* 7.8, H-3), 7.23 (1 H, d, *J* 7.8, H-4), 4.65 (1 H, m, H-6), 4.07 (1 H, d, *J* 6.4, H-5), 3.80 (3 H, s, H-10), 1.93-1.80 (1 H, m, H-7), 1.09 (3 H, d, *J* 6.8, H-8), 1.05 (3 H, d, *J* 6.8, H-9).

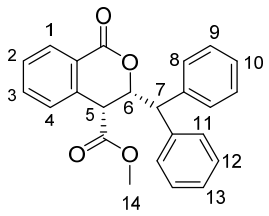
δ_C (100 MHz, $CDCl_3$): 169.5 (C=O), 165.6 (C=O), 136.1, 134.1, 130.3, 128.6, 127.3, 125.6, 83.9, 52.8, 46.3, 30.9, 19.3, 17.2.

ν_{max} (neat)/cm^{-1}: 2973, 1718, 1604, 1436, 1263, 1210, 1168, 1109, 1084, 983, 768, 714, 642.

HRMS (*m/z* -APCI): $[M+H]^+$ Found: 249.1122 $C_{14}H_{17}O_4$ Requires: 249.1121.

*$[\alpha]_D^{20}$ refers to a mixture of *cis*-**361**:*trans*-**361** in a 84:16 ratio

(3*R*,4*R*)-Methyl-3-benzhydryl-1-oxoisochromane-4-carboxylate (*cis*-**363**, *trans*-**363**, Table 4.3, entry 5)



Prepared according to general procedure H, using freshly distilled diphenylacetaldehyde (**440**, 43.6 μL, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 48 hours to give a diastereomeric mixture of carboxylic acids in a 87:13 ratio (*cis:trans*). After esterification, only the diastereomer *cis*-**363** was isolated and purified by flash column chromatography to give *cis*-**363** as a white solid (78.1 mg, 85%, 99% *ee*). M.p. 174-176. ºC, TLC (hexanes:EtOAc, 8/2 *v/v*): R_f = 0.67, $[\alpha]^{20}_D$ = -2.9 (c = 0.04, $CHCl_3$).

CSP-HPLC analysis. ACQUITY UPC^2, Trefoil AMY1, 2.5μm (3.0 x 150mm). ABPR: 1500 (psi). A (CO_2) = 97%/B (Ethanol/ACN/IPA 1:1:1, *v:v:v*) = 3%, 1.2 mL min^{-1}, 30 °C, UV detection at 254 nm, retention times: *cis*-**363** 2.0 min.

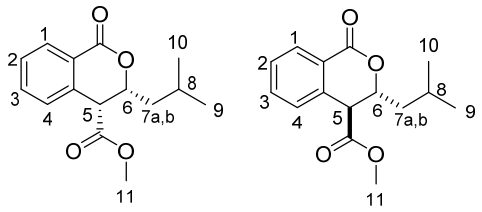
δ_H (400 MHz, $CDCl_3$): 8.15 (1 H, d, *J* 7.7, H-1), 7.56 (1 H, app. t, *J* 7.7, H-2), 7.50 (1 H, app. t, *J* 7.7, H-3), 7.43-7.38 (2 H, m, H-11), 7.38-7.25 (8 H, m, H-4, H-8, H-9, H-10 and H-12), 7.22 (1 H, t, *J* 7.3, H-13), 5.39 (1 H, dd, *J* 2.4, 10.9, H-6) ,4.59 (1 H, d, *J* 10.9, H-7), 3.75 (1 H, d, *J* 2.4, H-5), 3.66 (3 H, s, H-14).

δ_C (100 MHz, $CDCl_3$): 168.9 (C=O), 164.4 (C=O), 140.2, 140.1, 136.9, 133.7, 130.7, 129.1, 129.0, 128.6 (C x 2), 128.1, 127.6, 127.5, 126.8, 125.3, 79.9, 53.6, 52.4, 45.8.

ν_{max} (neat)/cm^{-1}: 3029, 1734, 1724, 1600, 1494, 1452, 1251, 1221, 1157, 1107, 1085, 996, 973, 749, 695, 592.

HRMS (*m/z* -APCI): $[M+H]^+$ Found: 373.1434 $C_{24}H_{21}O_4$ Requires: 373.1434.

Methyl-3-isopropyl-1-oxoisochromane-4-carboxylate (*cis*-**364**, *trans*-**364**, Table 4.3, entry 6)



Prepared according to general procedure H, using freshly distilled isovaleraldehyde (26.9 µL, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 18 h to give a diastereomeric mixture of carboxylic acids in a 78:22 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 80:20 hexanes:EtOAc, *cis*-**364** and *trans*-**364** were isolated combined as a white solid (58.7 mg, 91%). M.p. 95-97 °C, TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.27, $[\alpha]_D^{20}$ = -6.3 (*c* = 0.04, $CHCl_3$).* The enantiomeric excesses of *cis*-**364** and *trans*-**364** were found to be 99% and 91% respectively.

CSP-HPLC analysis. Chiralcel ODH (4.6 mm x 25 cm), hexane/IPA: 95/5, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: *cis*-**364** 18.4 min; *trans*-**364** 10.2 min (major enantiomer) and 12.2 min (minor enantiomer).

cis-**364**:

δ_H (400 MHz, $CDCl_3$): 8.19 (1 H, d, *J* 7.8, H-1), 7.59 (1 H, app. t, *J* 7.8, H-2), 7.51 (1 H, app. t, *J* 7.8, H-3), 7.33 (1 H, d, *J* 7.8, H-4), 4.72 (1 H, ddd, *J* 3.3, 4.5, 9.2, H-6), 3.83 (1 H, d, *J* 3.3, H-5), 3.70 (3 H, s, H-11), 2.10-2.01 (1 H, m, H-8), 1.87 (1 H, ddd, *J* 5.9, 9.2, 14.6, H-7a), 1.57 (1 H, ddd, *J* 4.5, 8.4, 14.6, H-7b), 1.01 (3 H, d, *J* 6.6, H-9), 0.98 (3 H, d, *J* 6.6, H-10).

δ_C (100 MHz, $CDCl_3$): 169.3 (C=O), 164.8 (C=O), 136.8, 133.7, 130.8, 129.0, 127.2, 125.4, 76.8, 52.6, 48.3, 41.5, 24.1, 22.9, 21.9.

trans-**364**:

δ_H (400 MHz, $CDCl_3$): 8.15 (1 H, d, *J* 7.4, H-1), 7.63-7.59 (1 H, m, H-2), 7.49-7.45 (1 H, m, H-3), 7.24 (1 H, d, *J* 7.3, H-4), 4.96 (1 H, ddd, *J* 4.5,

6.1, 9.2, H-6), 3.87 (1 H, d, *J* 6.1, H-5), 3.80 (3 H, s, H-11), 2.01-1.94 (1 H, m, H-8), 1.85 (1 H, ddd, *J* 5.9, 9.2, 14.6, H-7a), 1.35 (1 H, ddd, *J* 4.5, 8.4, 14.6, H-7b), 0.97 (3 H, d, *J* 6.6, H-9), 0.94 (3 H, d, *J* 6.6, H-10).

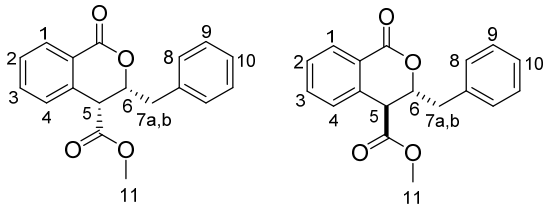
δ_C (100 MHz, $CDCl_3$): 170.7 (C=O), 164.9 (C=O), 135.8, 134.1, 130.4, 128.7, 127.4, 124.7, 77.2, 52.8, 48.8, 42.8, 24.3, 23.1, 21.5.

ν_{max} (neat)/cm^{-1}: 2956, 1719, 1605, 1459, 1311, 1264, 1163, 1113, 1087, 993, 948, 827, 711, 606, 567.

HRMS (*m/z* -APCI): $[M+H]^+$ Found: 263.1273 $C_{15}H_{19}O_4$ Requires: 263.1277.

*$[\alpha]_D^{20}$ refers to *cis*-**364** which was isolated after trituration of the diastereomeric mixture with isopropanol

Methyl-3-benzyl-1-oxoisochromane-4-carboxylate (*cis*-**365**, *trans*-**365**, Table 4.3, entry 7)



Prepared according to general procedure H, using freshly distilled phenylacetaldehyde (27.4 μL, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 48 h to furnish a diastereomeric mixture of carboxylic acids in a 84:16 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 80:20 hexanes:EtOAc, *cis*-**365** and *trans*-**365** were isolated combined as a white solid (67.1 mg, 92%). M.p. 68-70 °C, TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.41, $[\alpha]_D^{20}$ = -4.5 (*c* = 0.04, $CHCl_3$).* The enantiomeric excesses of *cis*-**365** and *trans*-**365** were both found to be 99%.

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: *cis*-**365** 48.0 min; *trans*-**365** 15.4 min.

cis-**365**:

δ_H (400 MHz, $CDCl_3$): 8.18 (1 H, d, *J* 6.5, H-1), 7.68 (1 H, app. t, *J* 6.5, H-3), 7.61 (1 H, app. t, *J* 6.5, H-2), 7.54-7.44 (5 H, m, H-8, H-9 and H-10), 7.43 (1 H, d, *J* 6.9, H-4), 5.34 (1 H, ddd, *J* 2.9, 6.7, 7.8, H-6), 4.51 (1 H, d, *J* 2.9, H-5), 4.44 (3 H, s, H-11), 4.06 (1 H, dd, *J* 6.7, 14.2, H-7b), 3.93 (1 H, dd, *J* 7.8, 14.2, H-7a).

δ_C (100 MHz, $CDCl_3$): 169.2 (C=O), 164.6 (C=O), 136.7, 135.7, 133.8, 130.7, 129.5, 129.1, 128.8, 127.4, 127.2, 125.4, 79.7, 52.7, 46.7, 38.9.

trans-**365**:

δ_H (400 MHz, $CDCl_3$): 8.19 (1 H, d, *J* 6.4, H-1), 7.75 (1 H, app. t, *J* 6.4, H-3), 7.61 (1 H, app. t, *J* 6.4, H-2), 7.54-7.44 (5 H, m, H-8, H-9 and H-10), 7.35 (1 H, d, *J* 6.4, H-4), 5.71-5.65 (1 H, m, H-6), 4.53 (1 H, d, *J* 5.2, H-5), 4.43 (3 H, s, H-11), 3.96 (1 H, dd, *J* 6.3, 14.1, H-7b), 3.71 (1 H, dd, *J* 7.8, 14.1, H-7a).

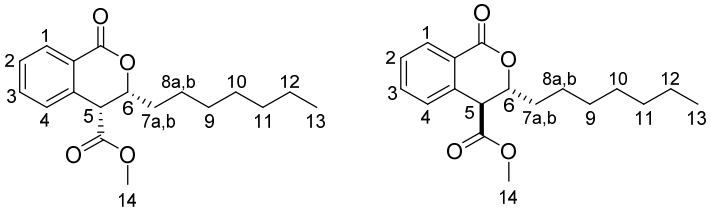
δ_C (100 MHz, $CDCl_3$): 169.2 (C=O), 164.6 (C=O), 135.5, 135.2, 134.3, 130.5, 129.5, 128.89, 128.83, 127.9, 127.3, 124.7, 79.4, 52.8, 46.5, 39.6.

ν_{max} (neat)/cm^{-1}: 3030, 2952, 1724, 1658, 1453, 1434, 1376, 1261, 1158, 1119, 1030, 979, 738, 698.

HRMS (*m/z* - ESI): $[M+Na]^+$ Found: 319.0945 $C_{18}H_{16}O_4Na$ Requires: 319.0940.

*$[\alpha]_D^{20}$ refers to a mixture of *cis*-**365**:*trans*-**365** in a 84:16 ratio

Methyl-3-heptyl-1-oxoisochromane-4-carboxylate (*cis*-**366**, *trans*-**366**, Table 4.3, entry 8)



Prepared according to general procedure H, using freshly distilled octanal (38.4 μL, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 18 h to give a diastereomeric mixture of carboxylic acids in a 79:21 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 90:10 hexanes:EtOAc, *cis*-**366** and *trans*-**366** were isolated combined as a white solid (70.4 mg, 94%). M.p. 50-55 ºC, TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.61, $[\alpha]_D^{20}$ = -3.2 (*c* = 0.05, $CHCl_3$).* The enantiomeric excesses of *cis*-**366** and *trans*-**366** were found to be 95% and 47% respectively.

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 98/2, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: *cis*-**366** 48.5 min (minor enantiomer) and 62.1 min (major enantiomer); *trans*-**366** 33.6 min (minor enantiomer) and 35.6 min (major enantiomer).

cis-**366**:

δ_H (400 MHz, $CDCl_3$): 8.17 (1 H, d, *J* 7.8, H-1), 7.61 (1 H, app. t, *J* 7.8, H-2), 7.50 (1 H, app. t, *J* 7.8, H-3), 7.32 (1 H, d, *J* 7.8, H-4), 4.63-4.59 (1 H, m, H-6), 3.88 (1 H, d, *J* 3.2, H-5), 3.69 (3 H, s, H-14), 1.96-1.86 (1 H, m, H-7a), 1.84-1.73 (1 H, m, H-7b), 1.69-1.54 (1 H, m, H-8a), 1.55-1.42 (1 H, m, H-8b), 1.41-1.20 (8 H, m, H-9, H-10, H-11 and H-12), 0.95-0.83 (3 H, m, H-13).

δ_C (100 MHz, $CDCl_3$): 169.3 (C=O), 164.8 (C=O), 136.8, 133.7, 130.7, 129.0, 127.2, 125., 78.7, 52.6, 47.9, 32.8, 31.7, 29.2, 29.0, 25.2, 22.7, 14.1.

trans-**366**:

δ_H (400 MHz, $CDCl_3$): 8.15 (1 H, d, *J* 8.0, H-1), 7.58 (1 H, app. t, *J* 8.0, H-2), 7.48 (1 H, app. t, *J* 8.0, H-3), 7.23 (1 H, d, *J* 8.0, H-4), 4.88 (1 H, ddd, *J* 3.8, 6.5, 12.5, H-6), 3.92 (1 H, d, *J* 6.5, H-5), 3.81 (3 H, s, H-14), 1.83-1.74 (1 H, m, H-7a), 1.69-1.54 (2 H, m, H-7b, H-8a), 1.55-1.42 (1 H, m, H-8b), 1.41-1.20 (8 H, m, H-9, H-10, H-11 and H-12), 0.95-0.83 (3 H, m, H-13).

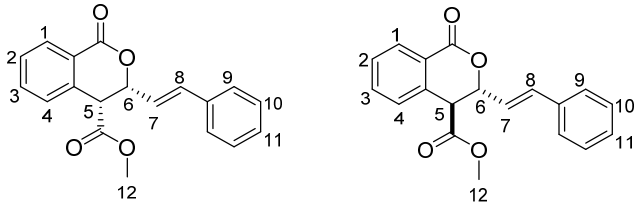
δ_C (100 MHz, $CDCl_3$): 170.7 (C=O), 163.9 (C=O), 135.9, 134.0, 130.5, 128.6, 127.3, 124.7, 79.1, 52.7, 48.4, 33.7, 31.6, 29.1, 29.03, 25.0, 22.6, 14.0.

ν_{max} (neat)/cm^{-1}: 3133, 3025, 1730, 1680, 1580, 1467, 1156, 1125, 1096, 1012, 790, 685, 705.

HRMS (*m/z* - APCI): $[M+H]^+$ Found: 305.1760 $C_{18}H_{25}O_4$ Requires: 305.1747.

*$[\alpha]_D^{20}$ refers to a mixture of *cis*-**366**:*trans*-**366** in a 79:21 ratio

Methyl-1-oxo-3-((*E*)-styryl)isochromane-4-carboxylate (*cis*-**367**,*trans*-**367**, Table 4.3, entry 9)



Prepared according to general procedure H, using freshly distilled cinnamaldehyde (31.0 µL, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 18 h to give a diastereomeric mixture of carboxylic acids in a 66:34 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 80:20 hexanes:EtOAc, *cis*-**367** and *trans*-**367** were isolated combined as a pale yellow oil (57.6 mg, 76%). TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.42, $[\alpha]_D^{20}$ = -6.0 (*c* = 0.03, $CHCl_3$).* The enantiomeric excesses of *cis*-**367** and *trans*-**367** were found to be 92% and 84% respectively.

CSP-HPLC analysis. ACQUITY UPC^2, Trefoil AMY1, 2.5µm (3.0 x 150mm). ABPR: 1500 (psi). A (CO_2) = 97%/B (Ethanol/ACN/IPA 1:1:1, *v:v:v*) = 3%, 1.2 mL min^{-1}, 30 °C, UV detection at 254 nm, retention times: *cis*-**367** 3.0 min (minor enantiomer) and 3.3 min (major enantiomer); *trans*-**367** 3.4 min (major enantiomer) and 3.7 min (minor enantiomer).

cis-**367**:

δ_H (400 MHz, $CDCl_3$): 8.22 (1 H, d, *J* 7.7, H-1), 7.63 (1 H, app. t, *J* 7.7, H-2), 7.54 (1 H, app. t, *J* 7.7, H-3), 7.44 (2 H, d, *J* 7.7, H-9), 7.42-7.29 (4 H, m, H-4, H-10 and H-11), 6.91 (1 H, d, *J* 16.0, H-8), 6.38 (1 H, dd, *J* 6.1, 16.0, H-7), 5.36 (1 H, ddd, *J* 1.4, 3.5, 6.1, H-6), 4.06 (1 H, d, *J* 3.5, H-5), 3.68 (3 H, s, H-12).

δ_C (100 MHz, $CDCl_3$): 168.8 (C=O), 164.2 (C=O), 136.3, 135.7, 134.05, 133.9, 130.8 129.2, 128.7, 128.5, 127.5, 126.8, 125.2, 123.1, 78.4, 52.6, 48.9.

trans-**367**:

δ_H (400 MHz, $CDCl_3$): 8.18 (1 H, d, *J* 7.9, H-1), 7.63 (1 H, app. t, *J* 7.9, H-2), 7.51 (1 H, app. t, *J* 7.9, H-3), 7.40 (2 H, d, *J* 7.9, H-9), 7.42-7.29 (4 H, m, H-4, H-10 and H-11), 6.79 (1 H, d, *J* 15.9, H-8), 6.20 (1 H, dd, *J* 6.8, 15.9, H-7), 5.60-5.54 (1 H, m, H-6), 4.11 (1 H, d, *J* 6.3, H-5), 3.80 (3 H, s, H-12).

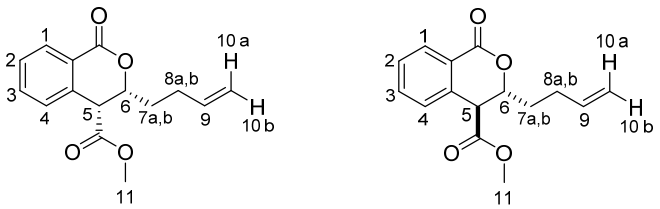
δ_C (100 MHz, $CDCl_3$): 170.1 (C=O), 163.7 (C=O), 135.4, 135.3, 135.2, 134.3, 130.5 128.9, 128.7, 128.6, 127.5, 126.8, 124.7, 123.9, 79.4, 52.9, 49.1.

ν_{max} (neat)/cm^{-1}: 2954, 1732, 1713, 1606, 1439, 1311, 1266, 1230, 1164, 1154, 1117, 710, 690, 607.

HRMS (*m/z* - APCI): $[M+Na]^+$ Found: 331.0943 $C_{19}H_{16}O_4Na$ Requires: 331.0940.

*$[\alpha]_D^{20}$ refers to a mixture of *cis*-**367**:*trans*-**367** in a 66:34 ratio

Methyl-3-(but-3-en-1-yl)-1-oxoisochromane-4-carboxylate (*cis*-**368**, *trans*-**368**, Table 4.3, entry 10)



Prepared according to general procedure H, using freshly distilled 4-pentenal (26.0 μL, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 18 h to give a diastereomeric mixture of carboxylic acids in a 74:26 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 85:15 hexanes:EtOAc, *cis*-**368** and *trans*-**368** were isolated combined as a pale yellow oil (61.4 mg, 96%). TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.47, $[\alpha]_D^{20}$ = -5.9 (*c* = 0.07, $CHCl_3$).* The enantiomeric excesses of *cis*-**368** and *trans*-**368** were found to be 97% and 90% respectively.

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: *cis*-**368** 10.5 min (minor enantiomer) and 12.8 min (major enantiomer); *trans*-**368** 8.4 min (minor enantiomer) and 9.0 min (major enantiomer).

cis-**368**:

δ_H (400 MHz, $CDCl_3$): 8.17 (1 H, d, *J* 7.3, H-1), 7.59 (1 H, app. t, *J* 7.3, H-2), 7.50 (1 H, app. t, *J* 7.3, H-3), 7.32 (1 H, d, *J* 7.3, H-4), 5.90-5.76 (1 H, m, H-9), 5.12 (1 H, dd, *J* 1.5, 17.1, H-10a), 5.04 (1 H, dd, *J* 1.5, 10.1, H-10b), 4.68 (1 H, ddd, *J* 3.3, 4.8, 8.7, H-6), 3.87 (1 H, d, *J* 3.3, H-5), 3.69 (3 H, s, H-11), 2.49-2.25 (2 H, m, H-8a and H-8b), 2.13-1.97 (1 H, m, H-7a), 1.95-1.81 (1 H, m, H-7b).

δ_C (100 MHz, $CDCl_3$): 169.2 (C=O), 164.7 (C=O), 136.7 (C x 2), 133.7, 130.7, 129.0, 127.3, 125.4, 116.1, 77.7, 52.6, 47.8, 31.8, 29.2.

trans-**368**:

δ_H (400 MHz, $CDCl_3$): 8.16 (1 H, d, *J* 7.6, H-1), 7.61 (1 H, app. t, *J* 7.6, H-2), 7.49 (1 H, app. t, *J* 7.6, H-3), 7.24 (1 H, d, *J* 7.6, H-4), 5.85-5.74 (1 H, m, H-9), 5.09 (1 H, dd, *J* 1.6, 17.3, H-10a), 5.03 (1 H, dd, *J* 1.6, 10.0, H-10b), 4.95 (1 H, ddd, *J* 4.0, 6.6, 10.5, H-6), 3.94 (1 H, d, *J* 6.6, H-5), 3.81 (3 H, s, H-11), 2.43-2.20 (2 H, m, H-8a and H-8b), 1.96-1.82 (1 H, m, H-7a), 1.77-1.64 (1 H, m, H-7b).

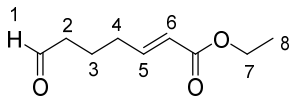
δ_C (100 MHz, $CDCl_3$): 170.6 (C=O), 163.8 (C=O), 136.6 (C x 2), 135.8, 134.1, 130.5, 128.7, 126.6, 124.6, 116.0, 78.3, 52.8, 48.4, 32.9, 29.1.

ν_{max} (neat)/cm^{-1}: 2951, 1720, 1640, 1604, 1458, 1435, 1240, 1159, 1116, 1086, 1030, 996, 916, 768, 709.

HRMS (*m/z* -APCI): $[M+H]^+$ Found: 261.1116 $C_{15}H_{17}O_4$ Requires: 261.1121.

*$[\alpha]_D^{20}$ refers to a mixture of *cis*-**368**: *trans*-**368** in a 74:26 ratio

(*E*)-Ethyl-7-oxohept-2-enoate (373)[217]

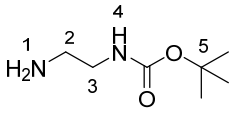


To an aqueous solution of glutaraldehyde (**371**, 15 mL, 166 mmol, 25% *w/v* in water) in CH_2Cl_2 (3 mL) was added a solution of (carboethoxymethylene)triphenylphosphorane (**372**, 5.78 g, 16.6 mmol) in CH_2Cl_2 (5 mL). The corresponding reaction mixture was allowed to stir at room temperature for 12 h, after which time EtOAc (30 mL) was added. The resulting solution was washed with water (20 mL) and then concentrated under reduced pressure. The crude product obtained was then purified by flash column chromatography eluting with 80:20 hexanes:EtOAc to furnish (*E*)-**373** as a colourless oil (1.24 g, 44%).

δ_H (400 MHz, $CDCl_3$): 9.79-9.74 (1 H, t, *J* 1.3, H-1), 6.93(1 H, dt, *J* 6.8, 15.7, H-5), 5.85 (1 H, d, *J* 15.7, H-6), 4.20 (2 H, q, *J* 7.1, H-7), 2.50 (2 H, dt, *J* 1.3, 13.2, H-2), 2.33-2.21 (2 H, m, H-4), 1.89-1.77 (2 H, m, H-3), 1.30 (3 H, t, *J* 7.1, H-8).

HRMS (*m/z* -ESI): $[M-H]^-$ Found:169.0707 $C_9H_{13}O_3$ Requires:169.0713.

***tert*-butyl (2-aminoethyl)carbamate (375)**[218]



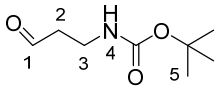
A 500 mL round-bottomed flask containing a magnetic stirring bar was charged with a solution of ethylenediamine (**374**, 5.6 mL, 83.3 mmol) in CH_2Cl_2 (25 mL). A solution of

di-*tert*-butyl dicarbonate (3.05 g, 14.0 mmol) in CH_2Cl_2 (200 mL) was then added dropwise over 3 h. The volatiles were removed *in vacuo* and the resulting oil was dissolved in a saturated aqueous solution of Na_2CO_3 (300 mL) and extracted with CH_2Cl_2 (2 x 150 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford **375** as colourless oil (1.59 g, 71%).

δ_H (400 MHz, $CDCl_3$): 4.90 (1 H, bs, H-4), 3.13 (2 H, m, H-3), 2.76 (2 H, m, H-2), 1.41 (9 H, s, H-5), 1.22 (2 H, bs, H-1).

HRMS (*m/z* - APCI): $[M+H]^+$ Found: 161.1289 $C_7H_{17}N_2O_2$ Requires: 161.1284.

***tert*-butyl (3-oxopropyl)carbamate (376)**[219]

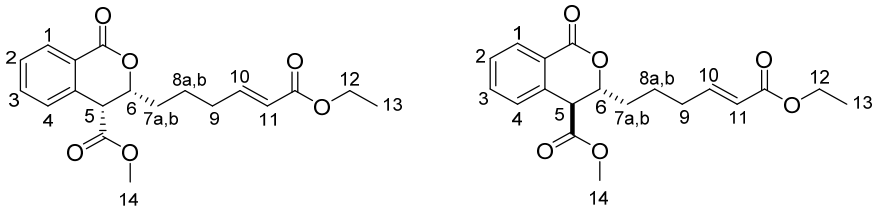


An oven-dried 50 mL round-bottomed flask containing a magnetic stirring bar under an argon atmosphere, was charged with a solution of DMSO (3 mL, 32.3 mmol) in CH_2Cl_2 (57 mL), followed by oxalyl chloride (1.4 mL, 16.1 mmol) at -78 °C. The resultant mixture was stirred for 15 min and a solution of **375** (1.71 g, 10.7 mmol) in CH_2Cl_2 (50 mL) was added dropwise. After 1 hour, triethylamine (7.5 mL, 53.8 mmol) was added at -78 °C and the corresponding solution was allowed to stir at room temperature for 30 min. The reaction mixture was then quenched with a 10% aqueous solution of HCl (100 mL) and extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$, then brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with 70:30 hexanes:EtOAc, to afford **376** as a yellow oil (1.50 g, 81%). TLC (hexanes:EtOAc 8:2, *v/v*): Rf = 0.42.

δ_H (400 MHz, $CDCl_3$): 9.79 (1 H, s, H-1), 4.73 (1 H, bs, H-4), 3.48-3.32 (2 H, m, H-3), 3.75-3.60 (2 H, m, H-2), 1.42 (9 H, s, H-5).

HRMS (*m/z* - APCI): $[M+Na]^+$ Found: 196.0936 $C_8H_{15}NO_3Na$ Requires: 196.0944.

Methyl-3-((*E*)-6-ethoxy-6-oxohex-4-en-1-yl)-1-oxoisochromane-4-carboxylate (*cis*-**369**, *trans*-**369**, Table 4.3, entry 11)



Prepared according to general procedure H, using aldehyde **373** (42.0 mg, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 18 h to give a diastereomeric mixture of carboxylic acids in a 73:27 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 85:15 hexanes:EtOAc, *cis*-**369** and *trans*-**369** were isolated combined as a pale yellow oil (71.6 mg, 84%). TLC (hexanes/EtOAc, 8:2 *v/v*): $R_f = 0.16$, $[\alpha]_D^{20} = -3.4$ ($c = 0.01$, $CHCl_3$).* The enantiomeric excesses of *cis*-**369** and *trans*-**369** were found to be 99% and 98% respectively.

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: *cis*-**369** 43.0 min; *trans*-**369** 20.9 min (minor enantiomer) and 23.5 min (major enantiomer).

cis-**369**:

δ_H (400 MHz, $CDCl_3$): 8.17 (1 H, d, *J* 7.1, H-1), 7.59 (1 H, app. t, *J* 7.1, H-2), 7.51 (1 H, app. t, *J* 7.1, H-3), 7.32 (1 H, d, *J* 7.1, H-4), 7.03-6.89 (1 H, m, H-10), 5.86 (1 H, d, *J* 15.5, H-11), 4.67-4.55 (1 H, m, H-6), 4.21 (2 H, q, *J* 7.1, H-12), 3.87 (1 H, d, *J* 2.8, H-5), 3.69 (3 H, s, H-14), 2.35-2.25 (2 H, m, H-9), 2.00-1.78 (2 H, m, H-7a and H-7b), 1.75.1.63 (2 H, m, H-8a and H-8b), 1.31 (3 H, t, *J* 7.1, H-13).

δ_C (100 MHz, $CDCl_3$): 169.1 (C=O), 165.5 (C=O), 164.5 (C=O), 147.8, 136.6, 133.8, 130.8, 129.1, 127.5, 125.4, 122.1, 78.3, 60.2, 52.6, 47.9, 32.2, 31.6, 23.8, 14.3.

trans-**369**:

δ_H (400 MHz, $CDCl_3$): 8.15 (1 H, d, *J* 7.8, H-1), 7.62 (1 H, app. t, H-2), 7.49 (1 H, app. t, H-3), 7.24 (1 H, d, *J* 7.8, H-4), 7.03-6.89 (1 H, m, H-10), 5.83 (1 H, d, *J* 14.5, H-11), 4.98-4.84 (1 H, m, H-6), 4.19 (2 H, q, *J* 7.1, H-12), 3.92 (1 H, d, *J* 6.9, H-5), 3.82 (3 H, s, H-14), 2.31-2.21 (2 H, m, H-9), 1.91-1.74 (2 H, m, H-7a and H-7b), 1.74-1.60 (2 H, m, H-8a and H-8b), 1.30 (3 H, t, *J* 7.1, H-13).

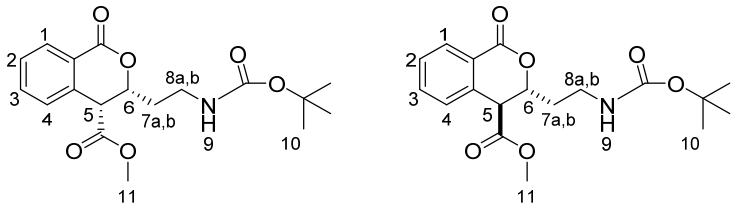
δ_C (100 MHz, $CDCl_3$): 170.5 (C=O), 166.5 (C=O), 163.7 (C=O), 147.7, 135.8, 134.2, 130.6, 128.8, 127.2, 124.5, 122.1, 78.6, 60.2, 52.8, 48.5, 33.0, 31.4, 23.4, 14.2.

ν_{max} (neat)/cm^{-1}: 2953, 1717, 1652, 1459, 1367, 1265, 1159, 1032, 976, 706, 625.

HRMS (*m/z* - ESI): $[M+Na]^+$ Found: 369.1309 $C_{19}H_{22}O_6Na$ Requires: 369.1308.

*$[\alpha]_D^{20}$ refers to a mixture of *cis*-**369**: *trans*-**369** in a 73:27 ratio

Methyl-3-(2-((tert-butoxycarbonyl)amino)ethyl)-1-oxoisochromane-4-carboxylate (*cis*-**370**, *trans*-**370**, Table 4.3, entry 12)



Prepared according to general procedure H, using aldehyde **376** (42.6 mg, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 24 h to give a diastereomeric mixture of carboxylic acids in a 84:16 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 70:30 hexanes:EtOAc, *cis*-**370** and *trans*-**370** were isolated combined as a pale yellow oil (64.4 mg, 75%). TLC (hexanes/EtOAc, 8:2 *v/v*): $R_f = 0.17$, $[\alpha]_D^{20} = -4.4$ (*c* =0.02, $CHCl_3$).* The enantiomeric excesses of *cis*-**370** and *trans*-**370** were found to be 99% *ee* and 81% *ee* respectively.

CSP-HPLC analysis. Chiralcel ODH (4.6 mm x 25 cm), hexane/IPA: 98/2, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: *cis*-**370** 364.7 min; *trans*-**370** 220.1 min (minor enantiomer) and 190.1 min (major enantiomer).

cis-**370**:

δ_H (400 MHz, $CDCl_3$): 8.17 (1 H, d, *J* 7.8, H-1), 7.60 (1 H, app. t, *J* 7.8, H-2), 7.51 (1 H, app. t, *J* 7.8, H-3), 7.34 (1 H, d, *J* 7.8, H-4), 4.88-4.77 (1 H, bs, H-9), 4.76-4.68 (1 H, m, H-6), 3.95 (1 H, d, *J* 3.5, H-5), 3.70 (3 H, s, H-11), 3.53-3.29 (2 H, m, H-8a and H-8b), 2.18-1.98 (2 H, m, H-7a and H-7b), 1.44 (9 H, s, H-10).

δ_C (100 MHz, $CDCl_3$): 169.2 (C=O), 164.5 (C=O), 156.1 (q), 136.7, 133.8, 130.7, 129.1, 127.4, 125.2, 76.5, 67.9, 52.6, 47.7, 36.9, 33.1, 28.3.

trans-**370**:

δ_H (400 MHz, $CDCl_3$): 8.15 (1 H, d, *J* 8.0, H-1), 7.63 (1 H, app. t, *J* 8.0, H-2), 7.49 (1 H, app. t, *J* 8.0, H-3), 7.27 (1 H, d, *J* 8.0, H-4), 5.04-4.96 (1 H, m, H-6), 4.88-4.77 (1 H, bs, H-9), 3.96 (1 H, d, *J* 5.6, H-5), 3.82 (3 H, s, H-11), 3.53-3.29 (2 H, m, H-8a and H-8b), 1.98-1.84 (2 H, m, H-7a and H-7b), 1.45 (9 H, s, H-10).

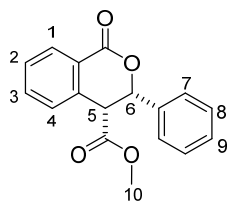
δ_C (100 MHz, $CDCl_3$): 170.3 (C=O), 163.5 (C=O), 155.9, 135.7, 134.3, 130.5, 128.8, 127.4, 124.4, 76.9, 68.5, 52.8, 48.2, 36.7, 33.7, 28.3.

ν_{max} (neat)/cm^{-1}: 3383, 2976, 1705, 1609, 1516, 1458, 1366, 1241, 1161, 1086, 1031, 994, 734, 605.

HRMS (*m/z* - ESI): $[M-H]^-$ Found: 348.1450 $C_{18}H_{22}NO_6$ Requires: 348.1447.

*$[\alpha]_D^{20}$ refers to a mixture of *cis*-**370**: *trans*-**370** in a 84:16 ratio

Methyl 1-oxo-3-phenylisochroman-4-carboxylate (*cis*-**152**, Table 4.4, entry 1)



Prepared according to general procedure H, using freshly distilled benzaldehyde (**135**, 25.0 μL, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was allowed to stir for 5 days to give a diastereomeric mixture of carboxylic acids in a 61:39 ratio (*cis*:*trans*). After esterification and purification by flash column chromatography, eluting with 80:20 hexanes:EtOAc, the diastereomer *cis*-**152** was isolated as a white solid (37.5 mg, 54%, 94% *ee*). M.p. 115-117 °C, TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.41, $[\alpha]_D^{20}$ = -4.3 (*c* = 0.02, $CHCl_3$).

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 18.6 min (minor enantiomer) and 23.6 min (major enantiomer).

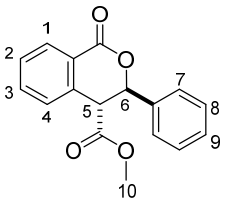
δ_H (400 MHz, $CDCl_3$): 8.26 (1 H, d, *J* 7.8, H-1), 7.64 (1 H, app. t, *J* 7.8, H-2), 7.56 (1 H, app. t, *J* 7.8, H-3), 7.52-7.48 (2 H, m, H-8), 7.44 (2 H, app. t, H-7), 7.42-7.36 (2 H, m, H-4, H-9), 5.80 (1 H, d, *J* 3.7, H-6), 4.16 (1 H, d, *J* 3.7, H-5), 3.47 (3 H, s, H-10).

δ_C (100 MHz, $CDCl_3$): 168.6 (C=O), 164.4 (C=O), 136.3, 136.2, 134.0, 131.0, 129.3, 128.7, 128.6, 127.3, 125.6, 125.3, 79.4, 52.3, 50.7.

ν_{max} (neat)/cm^{-1}: 2955, 1721, 1601, 1454, 1431, 1244, 1080, 997, 782, 701.

HRMS (*m/z* - APCI): $[M-H]^-$ Found: 281.0811 $C_{17}H_{13}O_4$ Requires: 281.0819.

Methyl 1-oxo-3-phenylisochroman-4-carboxylate (*trans*-**152**, Table 4.4, entry 1)[150]



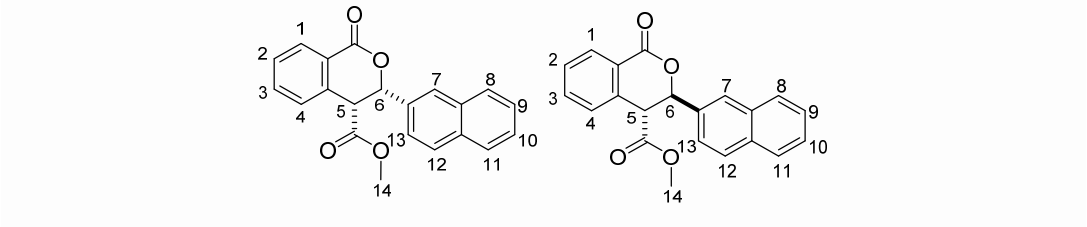
Prepared according to general procedure H, using freshly distilled benzaldehyde (**135**, 25 μL, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was allowed to stir for 5 days to give a diastereomeric mixture of carboxylic acids in a 61:39 ratio (*cis*:*trans*). After esterification and purification by flash column chromatography, eluting with 80:20 hexanes:EtOAc, the diastereomer *trans*-**152** was

isolated as a white solid (24.3 mg, 35%, 64% *ee*). M.p. 118-120 °C, TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.38. (lit.,[127,151] m.p. 129-132 °C).

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: *trans*-**152** 17.0 min (minor enantiomer) and 19.5 min (major enantiomer).

δ_H (400 MHz, $CDCl_3$): 8.19 (1 H, d, *J* 8.0, H-1), 7.60 (1 H, app. t, *J* 8.0, H-2), 7.49 (1 H, app. t, *J* 8.0, H-3), 7.44-7.30 (5 H, m, H-7, H-8 and H-9), 7.20 (1 H, d, *J* 8.0, H-4), 5.86 (1 H, d, *J* 8.3, H-6), 4.34 (1 H, d, *J* 8.3, H-5), 3.69 (3 H, s, H-10).

Methyl-3-(naphthalen-2-yl)-1-oxoisochromane-4-carboxylate (*cis*-**386**, *trans*-**386**, Table 4.4, entry 2)



Prepared according to general procedure H, using recrystallised 2-naphthaldehyde (**378**, 38.4 mg, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 7 days to give a diastereomeric mixture of carboxylic acids in a 49:51 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 90:10 hexanes:EtOAc, both diastereomers (*cis*-**386** and *trans*-**386**) were isolated combined as a pale yellow oil (68.7 mg, 84%). The enantiomeric excesses of *cis*-**386** and *trans*-**386** were found to be 34% and 62% respectively. TLC (hexanes/EtOAc, 8/2 *v/v*): R_f = 0.41.

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 95/5, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: *cis*-**386** 76.8 min (minor enantiomer) and 93.3 min (major enantiomer); *trans*-**386** 107.1 min (minor enantiomer) and 116.7 min (major enantiomer).

cis-**386**:

δ_H (400 MHz, $CDCl_3$): 8.29 (1 H, d, *J* 7.4, H-1), 8.04 (1 H, s, H-8), 7.95-7.86 (3 H, m, H-7, H-12 and H-11), 7.64 (1 H, app. t, *J* 7.4, H-2), 7.61-7.49 (4 H, m H-3, H-9, H-10 and H-13), 7.42 (1 H, d, *J* 7.6, H-4), 5.96 (1 H, d, *J* 3.8, H-6), 4.28 (1 H, d, *J* 3.8, H-5), 3.41 (3 H, s, H-14).

δ_C (100 MHz, $CDCl_3$): 168.6 (C=O), 164.4 (C=O), 136.4, 134.0, 133.5, 133.3, 133.2, 131.0, 129.3, 128.5, 128.3, 127.8, 127.4, 127.3, 126.5, 125.4, 124.5, 123.0, 79.4, 50.3, 50.6.

trans-**386**:

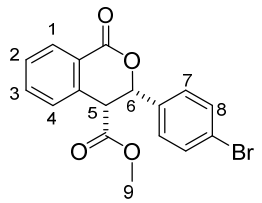
δ_H (400 MHz, $CDCl_3$): 8.23 (1 H, d, *J* 7.7, H-1), 7.90-7.81 (4 H, m, H-3, H-7, H-8, H-12), 7.62 (1 H, app. t, *J* 7.7, H-2), 7.55-7.48 (4 H, m, H-9, H-10, H-11, H-13), 7.23 (1 H, d, *J* 7.6, H-4), 6.06 (1 H, d, *J* 8.1, H-6), 4.48 (1 H, d, *J* 8.1, H-5), 3.69 (3 H, s, H-14).

δ_C (100 MHz, $CDCl_3$): 170.1 (C=O), 164.0 (C=O), 136.0, 134.4, 134.0, 133.4, 132.9, 130.7, 128.9, 128.7, 128.3, 127.7, 126.8, 126.7, 126.6, 126.4, 124.6, 123.8, 80.7, 52.7, 50.7.

ν_{max} (neat)/cm^{-1}: 3062, 2955, 1980, 1714, 1601, 1457, 1433, 1353, 1258, 1118, 1076, 1002, 955, 928, 862, 825, 733, 723, 689.

HRMS (*m/z* - ESI): $[M-H]^-$ Found: 331.0981 $C_{21}H_{15}O_4$ Requires: 331.0970.

Methyl-3-(4-bromophenyl)-1-oxoisochromane-4-carboxylate (*cis*-**387**, Table 4.4, entry 3)



Prepared according to general procedure H, using recrystallised *p*-bromobenzaldehyde (**379**, 45.5 mg, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 22 h to give a diastereomeric mixture of carboxylic acids in

a 60:40 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 85:15 hexanes:EtOAc, the diastereomer *cis*-**387** was isolated as a white solid (47.9 mg, 54%, 94% *ee*). M.p. 135-137 °C, TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.35, $[\alpha]_D^{20}$ = -7.6 (*c* = 0.03, $CHCl_3$).

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 95/5, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: 87.2 min (minor enantiomer) and 91.2 min (major enantiomer).

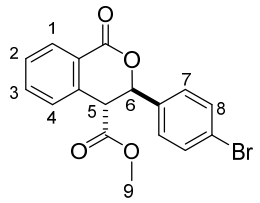
δ_H (400 MHz, $CDCl_3$): 8.25 (1 H, d, *J* 7.8, H-1), 7.65 (1 H, app. t, *J* 7.8, H-2), 7.60-7.54 (3 H, m, H-3 and H-8), 7.39 (3 H, m, H-4 and H-7), 5.75 (1 H, d, *J* 3.6, H-6), 4.14 (1 H, d, *J* 3.6, H-5), 3.49 (3 H, s, H-9).

δ_C (100 MHz, $CDCl_3$): 168.4 (C=O), 164.1 (C=O), 136.0, 135.2, 134.1, 131.8, 131.0, 129.4, 127.4, 127.3, 125.1, 122.8, 78.7, 52.5, 50.3.

ν_{max} (neat)/cm^{-1}: 3061, 3018, 2952, 1725, 1601, 1490, 1258, 1009, 822, 736, 692.

HRMS (*m/z* - ESI): $[M-H]^-$Found 358.9920 $C_{17}H_{12}O_4Br$ Requires 358.9924.

Methyl-3-(4-bromophenyl)-1-oxoisochromane-4-carboxylate (*trans*-**387**, Table 4.4, entry 3)[15]

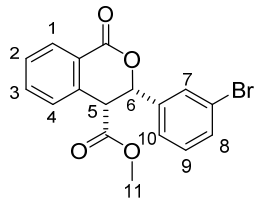


Prepared according to general procedure H, using recrystallised *p*-bromobenzaldehyde (**379**, 45.5 mg, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 22 h to give a diastereomeric mixture of carboxylic acids in a 60:40 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 85:15 hexanes:EtOAc, the diastereomer *trans*-**387** was isolated as a white solid (31.7 mg, 36%, 74% *ee*). M.p. 137-138 °C (lit.,[151] m.p. 138-140 °C), TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.38.

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 95/5, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: 70.0 min (minor enantiomer) and 80.7 min (major enantiomer).

δ_H (400 MHz, $CDCl_3$): 8.17 (1 H, d, *J* 7.9, H-1), 7.61 (1 H, app. t, *J* 7.9, H-2), 7.55-7.45 (3 H, m, H-3 and H-8), 7.28 (2 H, d, *J* 8.5, H-7), 7.19 (1 H, d, *J* 7.5, H-4), 5.80 (1 H, d, *J* 8.5, H-6), 4.28 (1 H, d, *J* 8.5, H-5), 3.71 (3 H, s, H-9).

Methyl 3-(3-bromophenyl)-1-oxoisochromane-4-carboxylate (*cis*-**388**, Table 4.4, entry 4)



Prepared according to general procedure H, using freshly distilled 3-bromobenzaldehyde (**380**, 28.7 μL, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 40 h to give a diastereomeric mixture of carboxylic acids in a 55:45 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 85:15 hexanes:EtOAc, the diastereomer *cis*-**388** was isolated as a white solid (39.1 mg, 44%, 93% *ee*). M.p. 92-94 °C, TLC (hexanes/EtOAc, 8/2 *v/v*): R_f = 0.50, $[\alpha]_D^{20}$ = -5.9 (*c* = 0.03, $CHCl_3$).

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 95/5, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 19.0 min (minor enantiomer) and 25.0 min (major enantiomer).

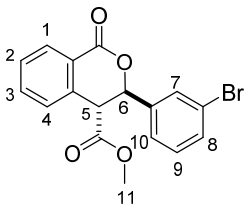
δ_H (400 MHz, $CDCl_3$): 8.26 (1 H, d, *J* 7.9, H-1), 7.69-7.59 (2 H, m, H-2 and H-7), 7.58-7.47 (2 H, m, H-3 and H-8), 7.45-733 (2H, m, H-9 and H-10) 7.30 (1 H, m, H-4), 5.83 (1 H, d, *J* 3.7, H-6), 4.15 (1 H, d, *J* 3.7, H-5), 3.50 (3 H, s, H-11).

δ_C (100 MHz, $CDCl_3$): 168.4 (C=O), 164.0 (C=O), 138.4, 135.9, 134.2, 131.9, 131.1, 130.2, 129.4, 128.8, 127.6, 125.1, 124.3, 122.8, 78.5, 52.5, 50.4.

ν_{max} (neat)/cm^{-1}: 2947, 1722, 1601, 1458, 1358, 1286, 1261, 1225, 1112, 1085, 1056, 996, 971, 989, 787, 717, 689, 638, 584.

HRMS (*m/z* - APCI): $[M+Na]^+$ Found: 382.9889 $C_{17}H_{13}BrO_4Na$ Requires: 382.9888.

Methyl 3-(3-bromophenyl)-1-oxoisochromane-4-carboxylate (*trans*-**388**, Table 4.4, entry 4)



Prepared according to general procedure H, using freshly distilled 3- bromobenzaldehyde (**380**, 28.7 μL, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 40 h to give a diastereomeric mixture of carboxylic acids in a 55:45 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 85:15 hexanes:EtOAc, the diastereomer *trans*-**388** was isolated as a white solid (35.3 mg, 39%, 72% *ee*). M.p. 100-105°C, TLC (hexanes/EtOAc, 8/2 *v/v*): R_f = 0.46, $[\alpha]_D^{20}$ = +8.8 (*c* = 0.05, $CHCl_3$).

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 16.7 min (minor enantiomer) and 18.8 min (major enantiomer).

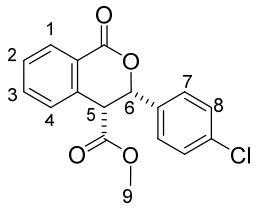
δ_H (400 MHz, $CDCl_3$): 8.21 (1 H, d, *J* 7.9, H-1), 7.64 (1 H, app. t, *J* 7.9, H-2), 7.59 (1 H, s, H-7), 7.55-7.52 (1 H, m, H-3), 7.51-7.49 (1 H, m, H-8), 7.36-7.31 (1 H, m, H-9), 7.28-7.20 (2 H, m, H-4 and H-10), 5.83 (1 H, d, *J* 8.7, H-6), 4.32 (1 H, d, *J* 8.7, H-5), 3.74 (3 H, s, H-11).

δ_C (100 MHz, $CDCl_3$): 169.8 (C=O), 163.7 (C=O), 138.8, 135.8, 134.6, 132.3, 130.7, 130.3, 129.9, 129.0, 126.7, 125.4, 124.3, 122.8, 79.7, 52.8, 50.7.

ν_{max} (neat)/cm^{-1}: 2940, 1720, 1601, 1455, 1348, 1285, 1260, 1235, 1112, 1075, 1054, 995, 971, 989, 783, 713, 687, 584.

HRMS (*m/z* - APCI): $[M+H]^+$ Found: 360.9887 $C_{17}H_{14}BrO_4$ Requires: 360.9888.

Methyl 3-(4-chlorophenyl)-1-oxoisochroman-4-carboxylate (*cis*-**389**, Table 4.4, entry 5)



Prepared according to general procedure H, using recrystallised 4-chlorobenzaldehyde (**381**, 34.6 mg, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 36 h to give a diastereomeric mixture of carboxylic acids in a 59:41 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 80:20 hexanes:EtOAc, the diastereomer *cis*-**389** was isolated as white solid (42.1 mg, 54%, 95% *ee*). M.p. 65-68 °C, TLC (hexanes/EtOAc, 8:2 *v/v*): $R_f = 0.70$, $[\alpha]^{20}_D = -11.6$ (*c* = 0.03, $CHCl_3$).

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 24.1 min (minor enantiomer) and 26.0 min (major enantiomer).

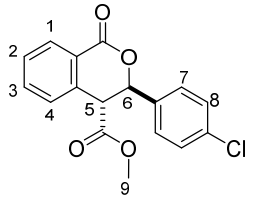
δ_H (400 MHz, $CDCl_3$): 8.25 (1 H, d, *J* 7.8, H-1), 7.60 (1 H, app. t, *J* 7.8, H-3), 7.56 (1 H, app. t, *J* 7.8, H-2), 7.49-7.32 (5 H, m, H-4, H-7 and H-8), 5.77 (1 H, d, *J* 3.4, H-6), 4.14 (1 H, d, *J* 3.4, H-5), 3,49 (3 H, s, H-9).

δ_C (100 MHz, $CDCl_3$): 168.4 (C=O), 164.1 (C=O), 136.0, 134.7, 134.6, 134.2, 131.0, 129.4, 128.9, 127.4, 127.0, 125.1, 78.6, 52.5, 50.4.

ν_{max} (neat)/cm^{-1}: 2953, 2926, 2862, 1736, 1709, 1602, 1459, 1261, 1001, 826, 740.

HRMS (*m/z* - ESI): $[M+H]^+$ Found: 317.0568 $C_{17}H_{14}O_4Cl$ Requires: 317.0580.

Methyl 3-(4-chlorophenyl)-1-oxoisochroman-4-carboxylate (*trans*-**389**, Table 4.4, entry 5)[150]

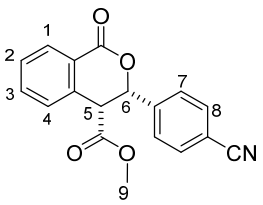


Prepared according to general procedure H, using recrystallised 4-chlorobenzaldehyde (**381**, 34.6 mg, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 36 h to give a diastereomeric mixture of carboxylic acids in a 59:41 ratio (*cis:trans*). After esterification and purification by flash column chromatography eluting with 80:20 hexanes:EtOAc, the diastereomer *trans*-**389** was isolated as a white solid (29.6 mg, 38%, 78% *ee*). M.p. 71-73 °C (lit.,[151] m.p. 70-72 °C), TLC (hexanes/EtOAc, 8:2 *v/v*): $R_f = 0.6$.

CSP-HPLC analysis Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 20.2 min (minor enantiomer) and 23.0 min (major enantiomer).

δ_H (400 MHz, $CDCl_3$): 8.18 (1 H, d, *J* 7.7, H-1), 7.61 (1 H, app. t, *J* 7.7, H-3), 7.50 (1 H, app. t, *J* 7.7, H-2), 7.39-7.29 (4 H, m, H-7 and H-8), 7.19 (1 H, d, *J* 7.7, H-4), 5.82 (1 H, d, *J* 8.7, H-6), 4.30 (1 H, d, *J* 8.7, H-5), 3.71 (3 H, s, H-9).

Methyl 3-(4-cyanophenyl)-1-oxoisochromane-4-carboxylate (*cis*-**390**, Table 4.4, entry 6)



Prepared according to general procedure H, using recrystallised 4-cyanobenzaldehyde (**382**, 32.3 mg, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 48h to give a diastereomeric mixture of carboxylic acids in a

58:42 ratio (*cis:trans*). After esterification and purification by flash column chromatography eluting with 75:25 hexanes:EtOAc, the diastereomer *cis*-**390** was isolated as a white solid (78.4 mg, 51%, 89% *ee*). M.p. 126-128°C, TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.25, $[\alpha]^{20}_D$ = -1.7 (*c* = 0.14, $CHCl_3$).

CSP-HPLC analysis. ACQUITY UPC^2, Trefoil AMY1, 2.5µm (3.0 x 150mm). ABPR: 1500 (psi). A (CO_2) = 97%/B (Ethanol/IPA 1:1, *v:v*) = 3%, 1.2 mL min^{-1}, 30 °C, UV detection at 254 nm, retention times: 3.5 min (major enantiomer) and 3.6 min (minor enantiomer).

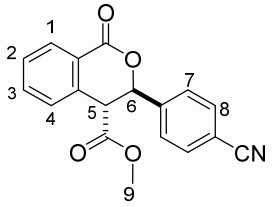
δ_H (400 MHz, $CDCl_3$): 8.20 (1 H, d, *J* 7.7, H-1), 7.71 (2 H, d, *J* 8.1, H-8), 7.65-7.58 (3 H, m, H-7 and H-2), 7.53 (1 H, app. t, *J* 7.7, H-3), 7.36 (1 H, d, *J* 7.7, H-4), 5.85 (1 H, d, *J* 3.6, H-6), 4.19 (1 H, d, *J* 3.6, H-5), 3.47 (3 H, s, H-9).

δ_C (100 MHz, $CDCl_3$): 168.1 (C=O), 163.6 (C=O), 141.3, 135.7, 134.3, 132.5, 131.1, 129.6, 127.5, 126.4, 124.9, 118.3, 112.7, 78.2, 52.5, 49.9.

ν_{max} (neat)/cm^{-1}: 2922, 2231, 1742, 1609, 1458, 1356, 1275, 1164, 1080, 1064, 971, 816, 704, 557.

HRMS (*m/z* - ESI): $[M-H]^-$ Found: 306.0761 $C_{18}H_{12}NO_4$ Requires: 306.0766.

Methyl 3-(4-cyanophenyl)-1-oxoisochromane-4-carboxylate (*trans*-**390**, Table 4.4, entry 6)



Prepared according to general procedure H, using recrystallised 4-cyanobenzaldehyde (**382**, 32.3 mg, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 48h to give a diastereomeric mixture of carboxylic acids in a 58:42 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 75:25 hexanes:EtOAc, the diastereomer *trans*-**390** was

isolated as yellow oil (67.6 mg, 42%, 60% *ee*). TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.23, $[\alpha]^{20}_D$ = +19.1 (*c* = 0.05, $CHCl_3$).

CSP-HPLC analysis. ACQUITY UPC^2, Trefoil CEL2, 2.5µm (3.0 x 150mm). ABPR: 1500 (psi). A (CO_2) = 97%/B (Ethanol/ACN 1:1, *v:v*) = 3%, 1.2 mL min^{-1}, 30 °C, UV detection at 254 nm, retention times: 3.1 min (minor enantiomer) and 3.4 min (major enantiomer).

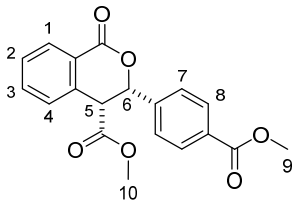
δ_H (400 MHz, $CDCl_3$): 8.21 (1 H, d, *J* 7.9, H-1), 7.70 (2 H, d, *J* 8.5, H-8), 7.65 (1 H, app. t, *J* 7.9, H-2), 7.58.7.51 (3 H, m, H-7 and H-3), 7.22 (1 H, d, *J* 7.7, H-4), 5.94 (1 H, d, *J* 8.5, H-6), 4.32 (1 H, d, *J* 8.5, H-5), 3.76 (3 H, s, H-9).

δ_C (100 MHz, $CDCl_3$): 169.6 (C=O), 163.4 (C=O), 141.7, 135.4, 134.7, 132.6, 130.8, 129.2, 127.6, 126.7, 124.2, 118.2, 113.2, 78.6, 52.9, 50.5.

ν_{max} (neat)/cm^{-1}: 2921, 2215, 1730, 1609, 1454, 1356, 1272, 1167, 1078, 1061, 956, 811, 701, 557.

HRMS (*m/z* - ESI): $[M-H]^-$ Found: 306.0757 $C_{18}H_{12}NO_4$ Requires: 306.0766.

Methyl 3-(4-(methoxycarbonyl)phenyl)-1-oxoisochromane-4-carboxylate (*cis*-**391**, Table 4.4, entry 7)



Prepared according to general procedure H, using recrystallised methyl 4-formylbenzoate (**383**, 40.4 mg, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 48 h to give a diastereomeric mixture of carboxylic acids in a 59:41 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 70:30 hexanes:EtOAc, the diastereomer *cis*-**391** was isolated as a white solid (46.0 mg, 55%, 88% *ee*). M.p. 144-146 °C. TLC (hexanes/EtOAc, 8:2 *v/v*): $R_f = 0.31$, $[\alpha]^{20}_D = -10.4$ (*c* = 0.04, $CHCl_3$).

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 33.0 min (major enantiomer) 53.2 min (minor enantiomer).

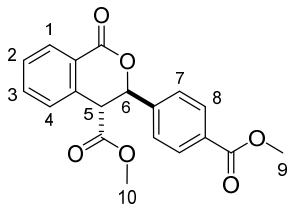
δ_H (400 MHz, $CDCl_3$): 8.26 (1 H, d, *J* 7.8, H-1), 8.13 (2 H, d, *J* 8.3, H-8), 7.67 (1 H, app. t, *J* 7.8, H-2), 7.63- 7.55 (3 H, m, H-7 and H-3), 7.42 (1 H, d, *J* 7.0, H-4), 5.85 (1 H, d, *J* 3.5, H-6), 4.19 (1 H, d, *J* 3.5, H-5), 3.97 (3 H, s, H-9), 3.47 (3 H, s, H-10).

δ_C (100 MHz, $CDCl_3$): 168.4 (C=O), 166.7 (C=O), 164.1 (C=O), 141.2, 136.0, 134.4, 131.1, 130.5, 129.9, 129.5, 126.5, 125.7, 125.1, 78.8, 52.5, 52.3, 50.5.

ν_{max} (neat)/cm^{-1}: 3016, 2162, 2030, 1748, 1611, 1428, 1280, 1250, 1193, 1072, 921, 870, 742, 642.

HRMS (*m*/*z*-APCI) $[M+Na]^+$ Found: 363.0839 $C_{19}H_{16}O_6Na$ Requires: 363.0839.

Methyl 3-(4-(methoxycarbonyl)phenyl)-1-oxoisochromane-4-carboxylate (*trans*-**391**, Table 4.4, entry 7)



Prepared according to general procedure H, using recrystallised methyl 4-formylbenzoate (**383**, 40.4 mg, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 48 h to give a diastereomeric mixture of carboxylic acids in a 59:41 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 70:30 hexanes:EtOAc, the diastereomer *trans*-**391** was isolated as a white solid (31.8 mg, 38%, 83% *ee*). M.p. 156-158°C, TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.32, $[\alpha]^{20}_D$= +6.3 (*c* = 0.04 $CHCl_3$).

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 32.2 min (minor enantiomer) and 37.9 min (major enantiomer).

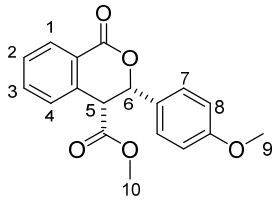
δ_H (400 MHz, $CDCl_3$): 8.21 (1 H, d, *J* 7.9, H-1), 8.06 (2 H, d, *J* 8.2, H-8), 7.64 (1 H, app. t, *J* 7.9, H-2), 7.57-7.45 (3 H, m, H-3 and H-7), 7.22 (1 H, d, *J* 7.9, H-4), 5.95 (1 H, d, *J* 8.2, H-6), 4.35 (1 H, d, *J* 8.2, H-5), 3.94 (3 H, s, H-9), 3.73 (3 H, s, H-10).

δ_C (100 MHz, $CDCl_3$): 169.8 (C=O), 166.5 (C=O), 163.7 (C=O), 141.4, 135.7, 134.7, 130.8, 130.7, 130.0, 129.0, 126.8, 126.7, 124.4, 80.0, 52.8, 52.3, 50.6.

ν_{max} (neat)/cm^{-1}: 3010, 2158, 2029, 1735, 1020, 1609, 1425, 1280, 1250, 1184, 1279, 1107, 1056, 1018, 921, 869, 736, 641.

HRMS (*m*/*z*-APCI) $[M+Na]^+$ Found: 363.0835 $C_{19}H_{16}O_6Na$ Requires: 363.0839.

Methyl 3-(4-methoxyphenyl)-1-oxoisochroman-4-carboxylate (*cis*-**392**, Table 4.4, entry 8)



Prepared according to general procedure H, using freshly distilled 4-methoxybenzaldehyde (**157**, 30 μL, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was allowed to stir for 48 h to give a diastereomeric

mixture of carboxylic acids in a 58:42 ratio (*cis:trans*). After esterification and purification by flash column chromatography eluting with 85:15 hexanes:EtOAc, the diastereomer *cis*-**392** was isolated as a white solid (26.9 mg, 35%, 91% *ee*). M.p. 75-77 °C, TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.52, $[\alpha]^{20}_D$= -7.1 (*c* = 0.04, $CHCl_3$).

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 97/3, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 66.7 min (minor enantiomer) and 69.8 min (major enantiomer).

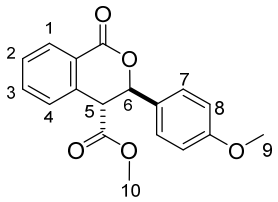
δ_H (400 MHz, $CDCl_3$): 8.25 (1 H, d, *J* 7.8, H-1), 7.63 (1 H, app. t, *J* 7.8, H-2), 7.55 (1 H, app. t, *J* 7.8, H-3), 7.44-7.35 (3 H, m, H-4, H-7), 6.95 (2 H, d, *J* 8.6, H-8), 5.75 (1 H, d, *J* 3.6, H-6), 4.12 (1 H, d, *J* 3.6, H-5), 3.85 (3 H, s, H-9), 3.50 (3 H, s, H-10).

δ_C (100 MHz, $CDCl_3$): 168.8 (C=O), 164.5 (C=O), 159.7, 136.3, 133.9, 130.9, 129.2, 128.2, 127.3, 126.9, 125.3, 113.9, 79.2, 55.3, 52.3, 50.8.

ν_{max} (neat)/cm^{-1}: 3012, 2959, 2930, 2834, 1710, 1604, 1518, 1248, 990, 734.

HRMS (*m/z* - ESI): $[M+Na]^+$ Found: 335.0888 $C_{18}H_{16}O_5Na$ Requires: 335.0895.

Methyl 3-(4-methoxyphenyl)-1-oxoisochroman-4-carboxylate (*trans*-**392**, Table 4.4, entry 8)[150]

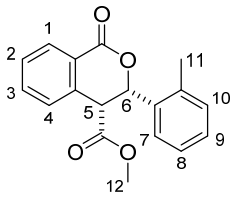


Prepared according to general procedure H, using freshly distilled 4-methoxybenzaldehyde (**157**, 30.0 μL, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was allowed to stir for 48 h to give a diastereomeric mixture of carboxylic acids in a 58:42 (*cis:trans*) ratio. After esterification and purification by flash column chromatography eluting with 85:15 hexanes:EtOAc, the diastereomer *trans*-**392** was isolated and purified as a white solid (23.1 mg, 30%, 40% *ee*). M.p. 80-82 °C, (lit.,[151] m.p. 82-84 °C), TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.57.

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 97/3, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 26.5 min (minor enantiomer) and 29.3 min (major enantiomer).

δ_H (400 MHz, $CDCl_3$): 8.18 (1 H, d, *J* 7.8, H-1), 7.60 (1 H, app. t, *J* 7.8, H-3), 7.49 (1 H, app. t, *J* 7.8, H-2), 7.31 (2 H, d, *J* 8.6, H-7), 7.19 (1 H, d, *J* 7.8, H-4), 6.88 (2 H, d, *J* 8.6, H-8), 5.77 (1 H, d, *J* 9.0, H-6), 4.34 (1 H, d, *J* 9.0, H-5), 3.80 (3 H, s, H-9), 3.69 (3 H, s, H-10).

Methyl 1-oxo-3-(o-tolyl) isochromane-4-carboxylate (*cis*-**393**, Table 4.4, entry 9)



Prepared according to general procedure H, using freshly distilled 2-methylbenzaldehyde (**49**, 28.4 µL, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 4 days to give a diastereomeric mixture of carboxylic acids in a 67:33 ratio (*cis:trans*). After esterification and purification by flash column chromatography eluting with 85:15 hexanes: EtOAc, the diastereomer *cis*-**393** was isolated as a white solid (42.3 mg, 58%, 95% *ee*). M.p. 108-110 °C. TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.38, $[\alpha]^{20}_D$ = -15.0 (*c* = 0.04, $CHCl_3$).

CSP-HPLC analysis. ACQUITY UPC^2, Trefoil AMY1, 2.5µm (3.0 x 150mm). ABPR: 1500 (psi). A (CO_2) = 99%/B (Ethanol/ACN/IPA 1:1:1, *v:v:v*) = 1%, 1.2 mL min^{-1}, 30 °C, UV detection at 254 nm, retention times: 3.2 min (minor enantiomer) and 3.4 min (major enantiomer).

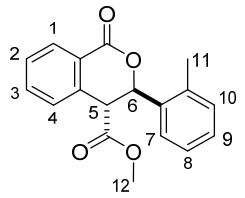
δ_H (400 MHz, $CDCl_3$): 8.28 (1 H, d, *J* 7.7, H-1), 7.67-7.61 (2 H, m, H-3, H-7), 7.57 (1 H, app. t, *J* 7.7, H-2), 7.37 (1 H, d, *J* 7.3, H-4) 7.33-7.28 (2 H, m, H-8, H-9), 7.25.7.22 (1 H, m, H-10), 5.96 (1 H, d, *J* 3.5, H-6), 4.11 (1 H, d, *J* 3.5, H-5), 3.47 (3 H, s, H-12), 2.39 (3 H, s, H-11).

δ_C (100 MHz, $CDCl_3$): 168.7 (C=O), 164.7 (C=O), 136.4, 134.2, 133.9, 133.5, 131.0, 130.6, 129.3, 128.6, 127.3, 126.4, 125.9, 125.4, 76.9, 52.3, 48.6, 19.1.

ν_{max} (neat)/cm^{-1}: 3071, 3024, 2952, 2929, 2844, 1718, 1602, 1457, 1250, 1003, 915, 736.

HRMS (*m/z* -ESI): $[M+Na]^+$ Found 319.0932. $C_{18}H_{16}O_4Na$ Requires 319.0940.

Methyl 1-oxo-3-(o-tolyl) isochromane-4-carboxylate (*trans*-**393**, Table 4.4, entry 9)[150]

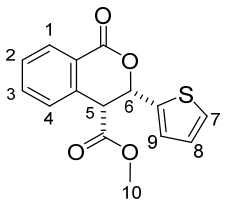


Prepared according to general procedure H, using freshly distilled 2-methylbenzaldehyde (**49**, 28.4 μL, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 4 days to give a diastereomeric mixture of carboxylic acids in a 67:33 ratio (*cis:trans*). After esterification and purification by flash column chromatography eluting with 85:15 hexanes:EtOAc, the diastereomer *trans*-**393** was isolated as a white solid (20.4 mg, 28%, 82% *ee*). M.p. 109-110 °C, (lit.,[151] 114-116 °C), TLC (hexanes/EtOAc, 8:2 *v/v*): $R_f = 0.41$.

CSP-HPLC analysis. Chiralcel ODH (4.6 mm x 25 cm), hexane/IPA: 83/17, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: 22.3 min (minor enantiomer) and 35.6 min (major enantiomer).

δ_H (400 MHz, $CDCl_3$): 8.20 (1 H, d, *J* 7.7, H-1), 7.62 (1 H, app. t, *J* 7.7, H-2), 7.51 (1 H, app. t, *J* 7.7, H-3), 7.31 (1 H, d, *J* 7.7, H-4) 7.28-7.13 (4 H, m, H-7, H-8, H-9 and H-10), 6.08 (1 H, d, *J* 8.7, H-6), 4.48 (1 H, d, *J* 8.7, H-5), 3.68 (3 H, s, H-12), 2.45 (3 H, s, H-11).

Methyl 1-oxo-3-(thiophen-2-yl)isochroman-4-carboxylate (*cis*-**394**, Table 4.4, entry 10)



Prepared according to general procedure H, using freshly distilled 2-thiophenecarboxaldehyde (**384**, 23 μL, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was allowed to stir for 6 days to give a diastereomeric mixture of carboxylic acids in a 56:44 ratio (*cis*:*trans*). After esterification and purification by flash column chromatography, eluting with 75:25 hexanes:EtOAc, the diastereomer *cis*-**394** was isolated as a brown solid (35.5 mg, 50%, 88% *ee*). M.p. 110-112 °C, TLC (hexanes/EtOAc, 8:2 *v/v*): $R_f = 0.35$, $[\alpha]^{20}_D = -3.2$ (*c* = 0.01, $CHCl_3$).

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 23.9 min (minor enantiomer) and 28.4 min (major enantiomer).

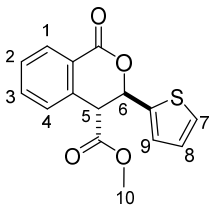
δ_H (400 MHz, $CDCl_3$): 8.24 (1 H, d, *J* 7.9, H-1), 7.65 (1 H, app. t, *J* 7.9, H-3), 7.57 (1 H, app. t, *J* 7.9, H-2), 7.44 (1 H, d, *J* 7.9, H-4), 7.38 (1 H, dd, *J* 1.2, 5.1, H-7), 7.19 (1 H, d, *J* 1.2, 3.7, H-9), 7.06 (1 H, dd, *J* 3.7, 5.1, H-8), 6.03 (1 H, d, *J* 3.6, H-6), 4.23 (1 H, d, *J* 3.6, H-5), 3.60 (3 H, s, H-10).

δ_C (100 MHz, $CDCl_3$): 168.6 (C=O), 163.9 (C=O), 138.4, 135.9, 134.1, 131.1, 129.4, 127.4, 126.8, 126.1, 125.6, 125.0, 52.7, 50.7, 30.9.

ν_{max} (neat)/cm^{-1}: 3104, 3011, 2951, 2925, 1727, 1703, 1605, 1459, 1431, 1359, 1332, 1226, 1081, 943, 714.

HRMS (*m/z* - APCI): $[M+H]^+$ Found: 289.0518 $C_{15}H_{13}O_4S$ Requires: 289.0529.

Methyl 1-oxo-3-(thiophen-2-yl)isochroman-4-carboxylate (*trans*-**394**, Table 4.4, entry 10)[150]

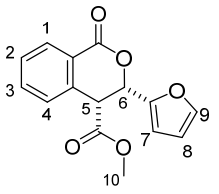


Prepared according to general procedure H, freshly distilled 2-thiophenecarboxaldehyde (**384**, 23 μL, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol).The reaction was allowed to stir for 5 days to give a diastereomeric mixture of carboxylic acids in a 56:44 ratio (*cis*:*trans*). After esterification and purification by flash column chromatography, eluting with 75:25 hexanes:EtOAc, the diastereomer *trans*-**394** was isolated as a white solid (26.2 mg, 37%, 57% *ee*). M.p. 110-112 °C (lit.,[129] 126-128 °C), TLC (hexanes/EtOAc, 8:2 *v/v*): $R_f = 0.36$.

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 30.3 min (minor enantiomer) and 32.9 min (major enantiomer).

δ_H (400 MHz, $CDCl_3$): 8.16 (1 H, d, *J* 7.9, H-1), 7.63 (1 H, app. t, *J* 7.9, H-3), 7.51 (1 H, app. t, *J* 7.9, H-2), 7.33-7.21 (2 H, m, H-4 and H-7), 7.09-7.01 (1 H, m, H-9), 6.96-6.89 (1 H, m, H-8), 6.19 (1 H, d, *J* 6.1, H-6), 4.35 (1 H, d, *J* 6.1, H-5), 3.75 (3 H, s, H-10).

Methyl 3-(furan-2-yl)-1-oxoisochromane-4-carboxylate (*cis*-**395**, Table 4.4, entry 11)



Prepared according to general procedure H, using freshly distilled furan-2-carboxaldehyde (**158**, 20.4 μL, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 3 days to give a diastereomeric mixture of carboxylic acids in a 74:26 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 75:25 hexanes:EtOAc, the diastereomer *cis*-**395**

was isolated as a white solid (45.5 mg, 68%, 46% *ee*). M.p. 105-108 °C, TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.58, $[\alpha]^{20}_D$ = -4.3 (*c* = 0.02, $CHCl_3$).

CSP-HPLC analysis. Chiralpak ODH (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 22.3 min (minor enantiomer) and 28.7 min (major enantiomer).

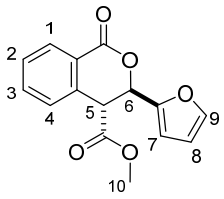
δ_H (400 MHz, $CDCl_3$): 8.23 (1 H, d, *J* 7.7, H-1), 7.64 (1H, app. t, *J* 7.7, H-2), 7.55 (1 H, app. t, *J* 7.7, H-3), 7.46 (1 H, d, *J* 1.8, H-9), 7.43 (1 H, d, *J* 7.7, H-4), 6.53 (1 H, d, *J* 3.3, H-7), 6.43 (1 H, dd, *J* 1.8, 3.3, H-8), 5.78 (1 H, d, *J* 3.6, H-6), 4.27 (1 H, d, *J* 3.6, H-5), 3.63 (3 H, s, H-10).

δ_C (100 MHz, $CDCl_3$): 168.9 (C=O), 163.8 (C=O), 148.7, 143.1, 135.9, 134.1, 131.0, 129.3, 127.4, 125.1, 110.6, 108.9, 73.9, 52.7, 47.8.

ν_{max} (neat)/cm^{-1}: 3139, 3115, 2945, 2844, 1734, 1712, 1601, 1462, 1435, 1256, 1121, 1003, 927, 742, 685.

HRMS (*m/z* - ESI): $[M+Na]^+$ Found: 295.0565 $C_{15}H_{12}O_5Na$ Requires: 295.0576.

Methyl 3-(furan-2-yl)-1-oxoisochromane-4-carboxylate (*trans*-**395**, Table 4.4, entry 11)[150]

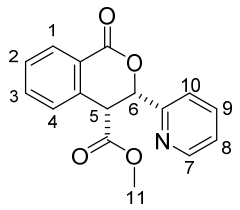


Prepared according to general procedure H, using freshly distilled furan-2-carboxaldehyde (**158**, 20.4 μL, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 3 days h to give a diastereomeric mixture of carboxylic acids in a 74:26 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 75:25 hexanes:EtOAc, diastereomer *trans*-**395** was isolated as a yellow solid (16.7 mg, 25%, 92% *ee*). M.p. 112-114 °C, (lit.,[151] 112-114 °C), TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.46.

CSP-HPLC analysis. Chiralpak ODH (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 23.3 min (major enantiomer) and 31.4 min (minor enantiomer).

δ_H (400 MHz, $CDCl_3$): 8.13 (1 H, d, *J* 7.8, H-1), 7.62 (1 H, app. t, *J* 7.8, H-2), 7.48 (1 H, app. t, *J* 7.8, H-3), 7.35 (1 H, s, H-9), 7.31 (1 H, d, *J* 7.8, H-4), 6.34-6.24 (2 H, m, H-7 and H-8), 6.00 (1 H, d, *J* 5.9, H-6), 4.46 (1 H, d, *J* 5.9, H-5), 3.76 (3 H, s, H-10).

Methyl 1-oxo-3-(pyridin-2-yl)isochromane-4-carboxylate (*cis*-**396**, Table 4.4, entry 12)



Prepared according to general procedure H, using freshly distilled pyridin-2 carboxaldehyde (**385**, 23.5 μL, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 4 days to give a diastereomeric mixture of carboxylic acids in a 61:39 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 70:30 hexanes:EtOAc, the diastereomer *cis*-**396** was isolated as a thick yellow oil (40.4 mg, 58%, 84% *ee*). TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.20, $[\alpha]^{20}_D$= -1.14 (c = 0.03, $CHCl_3$).

CSP-HPLC analysis. Chiralcel OJ-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 52.0 min (major enantiomer) and 78.3 min (minor enantiomer).

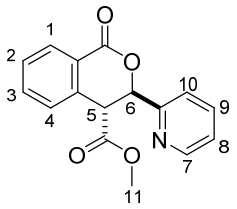
δ_H (400 MHz, $CDCl_3$): 8.62 (1 H, d, *J* 4.8, H-7), 8.24 (1 H, d, *J* 7.7, H-1), 7.86-7.78 (2 H, m, H-9 and H-10), 7.65 (1 H, app. t, *J* 7.7, H-2), 7.55 (1 H, app. t, *J* 7.7, H-3), 7.48 (1 H, d, *J* 7.7, H-4), 7.30 (1 H, m, H-8), 5.84 (1 H, d, *J* 3.6, H-6), 4.63 (1 H, d, *J* 3.6, H-5), 3.44 (3 H, s, H-11).

δ_C (100 MHz, $CDCl_3$): 168.8 (C=O), 164.0 (C=O), 156.0, 149.0, 137.0, 136.4, 134.2, 130.9, 129.2, 127.9, 125.1, 123.2, 120.7, 79.6, 52.3, 47.9.

ν_{max} (neat)/cm^{-1}: 2968, 1715, 1601, 1453, 1420, 1287,1253, 1119, 1002, 862, 824, 731, 720.

HRMS (*m/z* - ESI): $[M-H]^-$ Found: 282.0769 $C_{16}H_{12}NO_4$ Requires: 282.0766.

Methyl 1-oxo-3-(pyridin-2-yl)isochromane-4-carboxylate (*trans*-**396**, Table 4.4, entry 12)



Prepared according to general procedure H, freshly distilled pyridin-2 carboxaldehyde (**385**, 23.5 μL, 0.246 mmol) and homophthalic anhydride (**147**, 39.9 mg, 0.246 mmol). The reaction was stirred for 4 days to give a diastereomeric mixture of carboxylic acids in a 61:39 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 70:30 hexanes:EtOAc, the diastereomer *trans*-**396** was isolated as a thick yellow oil (22.3 mg, 32%, 25% *ee*). TLC (hexanes/EtOAc, 8/2 *v/v*): R_f = 0.30, $[\alpha]^{20}_D$ = +0.3 (c = 0.04, $CHCl_3$).

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 26.3 min (major enantiomer) and 32.8 min (minor enantiomer).

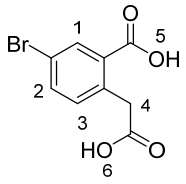
δ_H (400 MHz, $CDCl_3$): 8.52 (1 H, d, *J* 4.4, H-7), 8.13 (1 H, d, *J* 7.8, H-1), 7.69 (1 H, app. t, *J* 7.9, H-9), 7.57 (1 H, app. t, *J* 7.8, H-2), 7.53 (1 H, d, *J* 7.9, H-10), 7.43 (1 H, app. t, *J* 7.8, H-3), 7.33 (1 H, d, *J* 7.8, H-4), 7.23-7.17 (1 H, m, H-8), 6.13 (1 H, d, *J* 4.5, H-6), 4.89 (1 H, d, *J* 4.5, H-5), 3.80 (3 H, s, H-11).

δ_C (100 MHz, $CDCl_3$): 170.6 (C=O), 163.6 (C=O), 156.3, 149.0, 137.1, 135.2, 134.2, 130.2, 128.6, 128.3, 124.6, 123.2, 121.3, 79.9, 52.8, 47.0.

ν_{max} (neat)/cm^{-1}: 2969, 1715, 1601, 1455, 1425, 1289,1253, 1119, 1004, 862, 824, 733, 723.

HRMS (*m/z* -ESI): $[M-H]^-$ Found 282.0760 $C_{16}H_{12}NO_4$ Requires 282.0766.

5-bromo-2-(carboxymethyl)benzoic acid (**397**)[220]

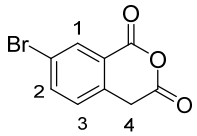


A 100 mL round-bottomed flask equipped with a condenser and containing a magnetic stirring bar was charged with homophthalic acid (**298**, 5.00 g, 27.0 mmol), potassium bromate (6.60 g, 40.0 mmol) and water (30 mL). The reaction mixture was then heated at 90 ºC and a solution of conc. H_2SO_4 (25 mL) in water (40 mL) was added over a period of 30 min. After completion of the addition, the reaction was stirred for 2 h at the same temperature, then cooled to room temperature. The solid formed was filtered, washed with water (3 x 25 mL), dried and recrystallised from EtOAc to furnish **397** as a white solid (2.20 g, 30%). Mp 216-217 °C, (lit.,[220] 216-217 °C).

δ_H (400 MHz, DMSO-d_6): 7.94 (1 H, s, H-1), 7.67 (1 H, d, *J* 8.0, H-2), 7.27 (1 H, d, *J* 8.0, H-3), 3.87 (2 H, s, H-4).

*The protic signals (H-5 and H-6) are not visible in DMSO-d_6.

7-Bromoisochroman-1,3-dione (**230**)[220]

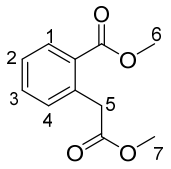


An oven-dried 50 mL round-bottomed flask fitted with a condenser was charged with 5-bromo-2-(carboxymethyl) benzoic acid (**397**, 1.00 g, 3.89 mmol). Freshly distilled acetyl chloride (15 ml) was added under an argon atmosphere and the reaction mixture was

heated at reflux temperature for 16 h. The reaction was then cooled to room temperature and the excess of acetyl chloride was removed *in vacuo*. The solid obtained was then triturated with Et_2O (10 mL), filtered and dried to give **230** as an off white solid (800 mg, 85%). M.p. 176-177 °C (lit.,[220] M.p. 171-173 °C).

δ_H (400 MHz, DMSO-d_6): 8.13 (1 H, d, *J* 2.0, H-1), 7.94 (1 H, dd, *J* 2.0, 8.3, H-2), 7.41 (1 H, d, *J* 8.3, H-3), 4.23 (2 H, s, H-4).

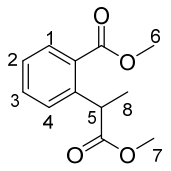
Methyl 2-(2-methoxy-2-oxoethyl)benzoate (399)[221]



In a 50 mL round-bottomed flask containing a magnetic stirring bar, homophthalic acid (**298**, 2.00 g, 11.1 mmol), was dissolved in MeOH (20 mL) and conc. H_2SO_4 (5 mL). The resultant solution was then heated at 80 °C for 4 h and then cooled to room temperature. A 2.0 M aqueous solution of NaOH (50 mL) was added and the reaction mixture was then extracted with EtOAc (2 × 20 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and the volatiles were removed under reduced pressure to afford **399** as a white solid (1.40 g, 62%). M.p. 48-49 °C (lit.,[222] m.p. 52-56 °C).

δ_H (400 MHz, DMSO-d_6): 8.02 (1 H, d, *J* 7.8, H-1), 7.74 (1 H, app. t, *J* 7.8, H-3), 7.52 (1 H, app. t, *J* 7.8, H-2), 7.43 (1 H, d, *J* 7.8, H-4), 3.98 (2 H, s, H-5), 3.78 (3 H, s, H-6), 3.60 (3 H, s, H-7).

Methyl 2-(1-methoxy-1-oxopropan-2-yl)benzoate (400)[222]



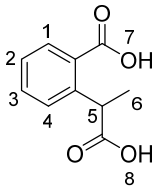
An oven-dried 50 mL round-bottomed flask containing a magnetic stirring bar was charged with freshly distilled diisopropylamine (747 µL, 5.30 mmol) and dry THF (3 mL) under an argon atmosphere. The solution was cooled to -78 °C and *n*-BuLi (1.6 M in THF, 3.3 mL, 5.30 mmol) was added. After 30 min, a solution of **399** (1.00 g, 4.80 mmol) in

dry THF (3.0 mL) was added dropwise *via* syringe. After stirring the solution for 1 h at -78 °C, MeI (597 µL, 9.49 mmol) was added dropwise and the reaction mixture allowed to stir for 1 h at -78 °C and then for 12 h at room temperature. The reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted with Et_2O (2 x 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to give a residue which was purified by flash column chromatography eluting with 90:10 hexanes:EtOAc to yield **400** as yellow oil (928 mg, 87%).

δ_H (400 MHz, $CDCl_3$): 7.98 (1 H, d, *J* 7.8, H-1), 7.72 (1 H, app. t, *J* 7.8, H-3), 7.57 (1 H, app. t, *J* 7.8, H-2), 7.30 (1 H, d, *J* 7.8, H-4), 4.58 (1 H, q, *J* 7.0, H-5), 3.87 (3 H, s, H-6), 3.66 (3 H, s, H-7), 1.54 (3 H, d, *J* 7.0, H-8).

HRMS (m/z -ESI): $[M+H]^+$ Found: 223.0890 $C_{12}H_{15}O_4$ Requires: 223.0891.

2-(1-carboxyethyl)benzoic acid (401)[236,237]

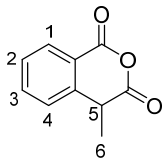


In a 50 mL round-bottomed flask containing a magnetic stirring bar, compound **400** (700 mg, 3.20 mmol) and KOH (1.80 g, 32.0 mmol) were dissolved in a mixture of MeOH (4 mL) and water (8.5 mL). The reaction mixture was then heated at 80 °C for 1 h and then cooled to room temperature. A 2.0 M aqueous solution of HCl (15 mL) was added and the reaction mixture was then extracted with Et_2O (2 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford a pale yellow solid which was triturated with Et_2O (5 mL) to give **401** as a white solid (600 mg, 90%). M.p. 138-140 °C (lit.,[236,237] m.p.146-161 °C).

δ_H (400 MHz, DMSO-d_6): 7.94 (1 H, d, *J* 7.8, H-1), 7.65 (1 H, app. t, *J* 7.8, H-3), 7.53-7.43 (2 H, m, H-2 and H-4), 4.25 (1 H, q, *J* 7.0, H-5), 1.54 (3 H, d, *J* 7.0, H-6).

* The protic signals (H-7 and H-8) are not visible in DMSO-d_6.

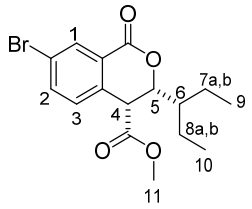
4-Methyl-isochromane-1,3-dione (402)[227]



An oven-dried 50 mL round-bottomed flask fitted with a condenser was charged with 2-(1-carboxyethyl)benzoic acid (**401**, 500 mg, 2.60 mmol). Freshly distilled acetyl chloride (10 ml) was added under an argon atmosphere and the reaction mixture was heated at reflux for 16 h. The reaction was then cooled to room temperature and the excess of acetyl chloride was removed under reduced pressure. The solid obtained was then triturated with Et_2O (2 mL), filtered and dried to furnish **402** as an off white solid (297 mg, 65%). M.p. 176-177 °C (lit.,[227] m.p. 171-173 °C).

δ_H (400 MHz, DMSO-d_6): 8.03 (1 H, d, *J* 8.4, H-1), 7.76 (1 H, app. t, *J* 8.4, H-3), 7.57-7.47, (2 H, m, H-2 and H-4), 4.33 (1 H, q, *J* 7.3, H-5), 3.30 (3 H, d, *J* 7.3, H-6).

Methyl -7-bromo-1-oxo-3-(pentan-3-yl)isochromane-4-carboxylate (*cis*-**404**, Table 4.5, entry 1)



Prepared according to general procedure H, using freshly distilled 2-ethylbutaraldehyde (**403**, 30.4 μL, 0.246 mmol) and anhydride **230** (59.3 mg, 0.246 mmol). The reaction was stirred for 9 days to give a diastereomeric mixture of carboxylic acids in a 84:16 ratio (*cis:trans*). After esterification, the diastereomer *cis*-**404** was isolated and purified by flash column chromatography, eluting with 90:10 hexanes:EtOAc to give *cis*-**404** as a white solid (62.0 mg, 71%, 99% *ee*). M.p. 72-75 °C, TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.67, $[\alpha]^{20}_D$ = -1.9 (c = 0.03, $CHCl_3$).

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 14.5 min (major enantiomer).

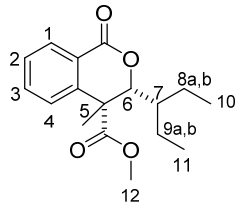
δ_H (400 MHz, $CDCl_3$): 8.30 (1 H, d, *J* 2.1, H-1), 7.70 (1 H, dd, *J* 2.1, 8.1, H-2), 7.23 (1 H, d, *J* 8.1, H-3), 4.42 (1 H, dd, *J* 2.9, 9.8, H-5), 3.97 (1 H, d, *J* 2.9, H-4), 3.69 (3 H, s, H-11), 1.89-1.79 (2 H, m, H-6 and H-7a), 1.67-1.57 (1 H, m, H-7b), 1.55-1.41 (2 H, m, H-8a and H-8b), 0.98-0.86 (6 H, m, H-9 and H-10).

δ_C (100 MHz, $CDCl_3$): 168.9 (C=O), 163.7 (C=O), 136.6, 135.9, 133.5, 128.8, 127.3, 122.9, 80.7, 52.7, 45.6, 41.6, 21.8, 20.8, 9.8, 9.6.

ν_{max} (neat)/cm^{-1}: 2959, 2888, 1716, 1601, 1468, 1414, 1255, 1227, 1166, 1130, 987, 907, 767, 638.

HRMS (*m/z* - APCI): $[M+Na]^+$ Found: 377.0361 $C_{16}H_{19}BrO_4Na$ Requires: 377.0358.

4-Methyl-1-oxo-3-(pentan-3-yl)isochromane-4-carboxylate (*cis*-**405**, Table 4.5, entry 2)



Prepared according to general procedure H, using freshly distilled 2-ethylbutaraldehyde (**403**, 30.4 μL, 0.246 mmol) and anhydride **402** (43.3 mg, 0.246 mmol). The reaction was stirred for 4 days to give a diastereomeric mixture of carboxylic acids in a 54:46 ratio (*cis:trans*). After esterification, the diastereomer *cis*-**405** was isolated and purified by flash column chromatography, eluting with 90:10 hexanes:EtOAc to give *cis*-**405** as a yellow oil (30.7 mg, 43%, 97% *ee*). TLC (hexanes/EtOAc, 8:2 *v/v*):R_f = 0.52, $[\alpha]^{20}_D$ = -1.43 (c = 0.04, $CHCl_3$).

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 8.1 min (minor enantiomer) and 9.6 min (major enantiomer).

δ_H (600 MHz, $CDCl_3$): 8.21 (1 H, d, *J* 8.2, H-1), 7.62 (1 H, app. t, *J* 8.2, H-2), 7.48 (1 H, app. t, *J* 8.2, H-3), 7.42 (1 H, d, *J* 8.2, H-4), 4.45 (1 H, d, *J* 1.2, H-6), 3.63 (3 H, s, H-12), 1.77-1.71 (1 H, m, H-7),

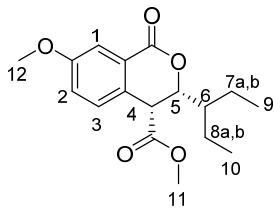
1.67-1.70 (4 H, m, H-5 and H-8a), 1.60-1.51 (1 H, m, H-8b), 1.44-1.35 (2 H, m, H-9a and H-9b), 0.98-0.93 (6 H, m, H-10 and H-11).

δ_C (100 MHz, $CDCl_3$): 172.5 (C=O), 165.2 (C=O), 142.5, 133.7, 130.7, 128.2, 125.6, 124.6, 84.7, 52.6, 46.8, 41.4, 24.1, 21.1, 19.8, 12.5, 11.7.

ν_{max} (neat)/cm^{-1}: 2964, 2897, 1713, 1601, 1465, 1413, 1252, 1224, 1160, 1130, 984, 903, 764, 632.

HRMS (*m/z* - ESI): $[M+Na]^+$ Found: 313.1405 $C_{17}H_{22}O_4Na$ Requires: 313.1410.

Methyl 7-methoxy-1-oxo-3-(pentan-3-yl)isochromane-4-carboxylate (*cis*-**406**, Table 4.5, entry 3)



Prepared according to general procedure H, using freshly distilled 2-ethylbutaraldehyde (**403**, 30.4 μL, 0.246 mmol) and anhydride **398** (47.3 mg , 0.246 mmol). The reaction was stirred for 10 days to give a diastereomeric mixture of carboxylic acids in a 80:20 ratio (*cis:trans*). After esterification, the diastereomer *cis*-**406** was isolated and purified by flash column chromatography, eluting with 85:15 hexanes:EtOAc to give *cis*-**406** as a white solid (50.5 mg, 67%, 57% *ee*). M.p. 85-87 °C, TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.73, $[\alpha]^{20}_D$ = -3.0 (c = 0.03, $CHCl_3$).

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 9.3 min (minor enantiomer) and 17.6 (major enantiomer).

δ_H (600 MHz, $CDCl_3$): 7.65 (1 H, d, *J* 2.8 H-1), 7.25 (1 H, d, *J* 8.3, H-3), 7.14 (1 H, dd, *J* 2.8, 8.3, H-2), 4.43 (1 H, dd, *J* 3.1, 9.7, H-5), 3.94 (1 H, d, *J* 3.1, H-4), 3.88 (3 H, s, H-12), 3.67 (3 H, s, H-11), 1.88-1.76 (2 H, m, H-6 and H-8a), 1.70-1.58 (2 H, m, H-7a and H-

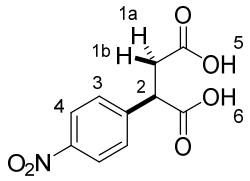
7b), 1.52-1.40 (1 H, m, H-8b), 0.95-0.88 (6 H, m, H-9 and H-10).

δ_C (100 MHz, $CDCl_3$): 169.8 (C=O), 165.1 (C=O), 159.9, 129.5, 128.5, 126.5, 121.4, 113.4, 80.8, 55.7, 52.7, 45.3, 41.6, 19.6, 19.7, 9.7, 9.6.

ν_{max} (neat)/cm^{-1}: 2963, 2847, 1718, 1611, 1500, 1428, 1312, 1276, 1229, 1164, 1074, 1036, 861, 786, 643.

HRMS (*m/z* - ESI): $[M+Na]^+$ Found: 329.1370 $C_{17}H_{22}O_5Na$ Requires: 329.1359.

2-(4-Nitrophenyl)succinic acid (**408**)[167]

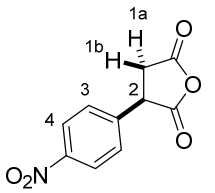


A 50 mL three-necked round-bottomed flask containing a magnetic stirring bar and equipped with a thermometer was charged with fuming HNO_3 (15 mL) and cooled to 0 °C. Phenylsuccinic acid (**407**, 2.00 g, 25.7 mmol) was added portionwise and the resultant solution was allowed to stir at 0 °C for 2 h. Crushed ice (15.0 g) and water (20 mL) were added to the reaction mixture. The white precipitate formed was filtered, washed with water, dried, and then recrystallised from water to obtain **408** as a white solid (3.40 g, 56%). M.p. 228-230 °C. (lit.,[167] m.p. 233-235 °C).

δ_H (400 MHz, DMSO-d_6):* 8.16 (2 H, d, *J* 8.6, H-4), 7.56 (2 H, d, *J* 8.6, H-3), 4.06 (1 H, dd, *J* 5.4, 9.5, H-2), 2.97 (1 H, dd, *J* 9.5, 17.1, H-1b), 2.61 (1 H, dd, *J* 5.4, 17.1, H-1a).

*The protic signals (H-5 and H-6) are not visible in DMSO-d_6.

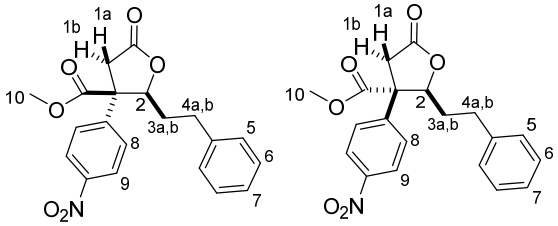
3-(4-Nitrophenyl)dihydrofuran-2,5-dione (**211**)[167]



A 50 mL round-bottomed flask containing a magnetic stirring bar was charged with **408** (2.00 g, 8.36 mmol). The apparatus was then fitted with a condenser and placed under an argon atmosphere. Freshly distilled acetyl chloride (15 mL) was added and the reaction mixture was heated at reflux temperature for 16 h. The acetyl chloride was then removed *in vacuo* to obtain a yellow oil that was purified through a plug of silica eluting with 50:50 hexanes:EtOAc followed by several azeotropic distillations with $CHCl_3$ on a rotary evaporator (5 x 5 mL) to obtain **211** as a white solid (1.20 g, 68%). M.p.66-68 °C.

δ_H (400 MHz, DMSO-d_6):* 8.22 (2 H, d, *J* 8.7, H-4), 7.74 (2 H, d, *J* 8.7, H-3), 4.84 (1 H, dd, *J* 8.3, 10.2, H-2), 3.44 (1 H, dd, *J* 10.2, 18.3, H-1b), 3.32 (1 H, dd, *J* 8.3, 18.3, H-1a).

Methyl 3-(4-nitrophenyl)-5-oxo-2-phenethyltetrahydrofuran-3-carboxylate (*cis*-**214**, *trans*-**214**, Table 4.6, entry 4)[167]



Prepared according to general procedure H, using freshly distilled hydrocinnamaldehyde (**202**, 32.4 μL, 0.246 mmol) and anhydride **211** (54.3 mg, 0.246 mmol). The reaction was stirred for 7 days at -75 °C to give a diastereomeric mixture of carboxylic acids in a 86:14 ratio (*cis:trans*). After esterification and purification by flash column chromatography eluting with 80:20 hexanes:EtOAc, *cis*-**214** and *trans*-**214** were isolated combined as a pale yellow oil (75.4 mg, 83%, 74% *ee*). TLC (hexanes/EtOAc, 8/2 *v/v*): R_f = 0.41.

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 85/15, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: *cis*-**214** 35.4 (minor enantiomer) and 44.3 min (major enantiomer)

cis-**214**:

δ_H (600 MHz, $CDCl_3$): 8.15 (2 H, d, *J* 8.4, H-9), 7.39-7.31 (2 H, m, H-8), 7.31-7.22 (3 H, m, H-6 and H-7), 7.22-7.15 (2 H, m, H-5), 4.88 (1 H, dd, *J* 1.6, 11.0, H-2), 3.75 (3 H, s, H-10), 3.52 (1 H, d, *J* 17.1,

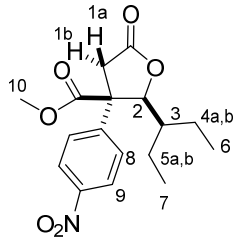
H-1a), 3.10-3.00 (1 H, m, H-4a), 2.90-2.78 (1 H, m, H-4b), 2.75 (1 H, d, *J* 17.1, H-1b), 2.22-2.11 (1 H, m, H-3a), 2.02-1.90 (1 H, m, H-3b).

trans-**214**:

δ_H (600 MHz, $CDCl_3$): 8.21 (2 H, d, *J* 8.5, H-9), 7.35 (2 H, d, *J* 8.5, H-8), 7.31-7.22 (2 H, m, H-6), 7.24-7.13 (1 H, m, H-7), 7.10 (2 H, d, *J* 7.4, H-5), 5.14 (1 H, dd, *J* 1.6, 10.9, H-2), 3.76 (3 H, s, H-10), 3.37 (1 H, d, *J* 17.4, H-1b), 3.14 (1 H, d, *J* 17.4, H-1a), 2.90-2.78 (1 H, m, H-4a), 2.72-2.63 (1 H, m, H-4b), 1.80-1.65 (1 H, m, H-3a), 1.37-1.20 (1 H, m, H-3b).

HRMS (*m/z* - ESI): $[M-H]^-$ Found: 368.1136 $C_{20}H_{18}NO_6$ Requires: 368.1134.

Methyl 3-(4-nitrophenyl)-5-oxo-2-(pentan-3-yl)tetrahydrofuran-3-carboxylate (*cis*-**409**, Scheme 4.9)



Prepared according to general procedure H, using freshly distilled 2-ethylbutyraldehyde (**403**, 30.3 µL, 0.246 mmol) and anhydride **211** (54.4 mg, 0.246 mmol). The reaction was stirred for 13 days to give a diastereomeric mixture of carboxylic acids in a 87:13 ratio (*cis:trans*). After esterification, the diastereomer *cis*-**409** was isolated and purified by flash column chromatography, eluting with 75:25 hexanes:EtOAc, to give *cis*-**409** as a yellow oil (43.7 mg, 53%, 95% *ee*). TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.69, $[\alpha]^{20}_D$ = +5.0 (c = 0.01, $CHCl_3$).

CSP-HPLC analysis. ACQUITY UPC^2, Trefoil CEL2, 2.5µm (3.0 x 150mm). ABPR: 1500 (psi). A (CO_2) = 97%/B (Ethanol/ACN 1:1, *v:v*) = 3%, 1.2 mL min^{-1}, 30 °C, UV detection at 254 nm, retention times: 3.7 min (minor enantiomer) and 3.8 min (major enantiomer.

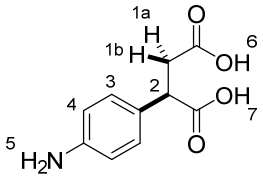
δ_H (400 MHz, $CDCl_3$): 8.27 (2 H, d, *J* 8.2, H-9), 7.47 (2 H, d, *J* 8.2, H-8), 5.06 (1 H, d, *J* 3.4, H-2), 3.81 (3 H, s, H-10), 3.59 (1 H, d, *J* 17.1, H-1b), 2.72 (1 H, d, *J* 17.1, H-1a), 1.84-1.76 (1 H, m, H-3), 1.55-1.46 (2 H, m, H-4a and H-5a), 1.47-1.41 (2 H, m, H-4b, H-5b), 1.02-0.93 (6 H, m, H-6 and H-7).

δ_C (100 MHz, $CDCl_3$): 172.8 (C=O), 171.0 (C=O), 147.4 (C×2), 127.2, 124.3, 85.9, 57.9 (q), 53,3, 42.8, 41.6, 23.1, 20.6, 11.2, 11.0.

ν_{max} (neat)/cm^{-1}: 2922. 2962, 1786, 1722, 1600, 1512, 1409, 1512, 1347, 1233, 1206, 1185, 1012, 949, 853, 798, 703.

HRMS (*m/z* -APCI): $[M+H]^+$ Found: 336.1438 $C_{17}H_{22}NO_6$ Requires: 336.1441.

2-(4-Aminophenyl)succinic acid (410)[167]

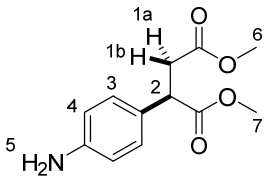


An oven-dried 100 mL round-bottomed flask, was charged with **408** (3.00 g, 12.5 mmol) followed by MeOH (20 mL) and 10% Pd/C (2 mol%). The flask was evacuated, placed under a hydrogen atmosphere and allowed to stir for 3 h at room temperature. The flask was then evacuated and filled with argon atmosphere. Water (25 mL) was added, the reaction mixture was heated at 70 °C for 10 minutes and then filtered hot through a pad of Celite and washed with hot water (5 mL). The filtrate was allow to cool to room temperature and the precipitate formed was collected by suction filtration and dried *in vacuo* to obtain **410** as a pale yellow solid (1.90 g, 74%). M.p. 200-202 °C (lit.,[167] m.p. 202-204 °C).

δ_H (400 MHz, DMSO-d_6):*6.91 (2 H, d, *J* 8.3, H-3), 6.49 (2 H, d, *J* 8.3, H-4), 3.66 (1 H, dd, *J* 5.0, 10.5, H-2), 2.86 (1 H, dd, *J* 10.5, 16.9, H-1b), 2.42 (1 H, dd, *J* 5.0, 16.9, H-1a).

* The protic signals (H-5, H-6 and H-7) are not visible in DMSO-d_6.

Dimethyl 2-(4-aminophenyl)succinate (411)[167]

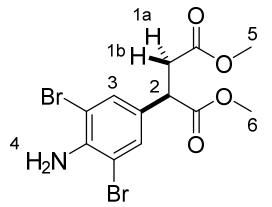


In a 100 mL round-bottomed flask containing a magnetic stirring bar, **410** (1.20 g, 5.70 mmol) was dissolved in anhydrous MeOH (10 mL) under an argon atmosphere. Freshly distilled thionyl chloride (1.5 mL, 20.0 mmol) was added dropwise *via* syringe at 0 °C. The flask was then fitted with a condenser and the reaction mixture was heated at 70 °C for 16 h. The reaction was allowed to cool to room temperature and the excess of thionyl chloride was quenched by addition of a saturated aqueous solution of $NaHCO_3$. The solvent was then removed *in vacuo* and the mixture obtained was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford **411** as a peach coloured solid (1.12 g, 81%). M.p. 108-110 °C, (lit.,[167] m.p. 110-112 °C).

δ_H (400 MHz, $CDCl_3$):* 7.02 (2 H, d, *J* 8.4, H-3), 6.60 (2 H, d, *J* 8.4, H-4), 3.94 (1 H, dd *J* 5.4, 10.1, H-2), 3.63 (6 H, s, H-6 and H-7), 3.12 (1 H, dd, *J* 10.1, 16.9, H-1b), 2.61 (1 H, dd, *J* 5.4, 16.9, H-1a).

* The protic signal (H-5) is not visible in $CHCl_3$

Dimethyl 2-(4-amino-3,5-dibromophenyl)succinate (412)[167]



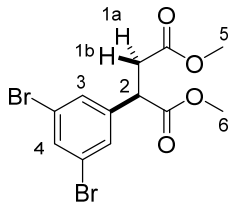
An oven-dried 50 mL round-bottomed flask containing a magnetic stirring bar was charged with **411** (1.49 g, 6.30 mmol) and acetic acid (15 mL). Bromine (798 μL, 15.5 mmol) was added dropwise at room temperature and the reaction mixture was allowed to stir for 1 h. After quenching the bromine in excess by adding a saturated aqueous solution of $Na_2S_2O_3$, a 10% aqueous solution of $NaHCO_3$ was added until pH = 8 was reached. The reaction mixture was then extracted with CH_2Cl_2 (3 x 50 mL), the combined organic

phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to obtain **412** as a yellow oil (1.59 g, 64%).

δ_H (400 MHz, $CDCl_3$): 7.31 (2 H, s, H-3), 4.55 (2 H, bs, H-4), 3.89 (1 H, dd, *J* 5.6, 9.7, H-2), 3.66 (3 H, s, H-6), 3.65 (3 H, s, H-5), 3.13 (1 H, dd, *J* 9.7, 17.0, H-1b), 2.63 (1 H, dd, *J* 5.6, 17.0, H-1a).

HRMS (*m/z* - ESI): $[M+Na]^+$ Found: 415.9126 $C_{12}H_{13}Br_2NO_4Na$ Requires: 415.9109.

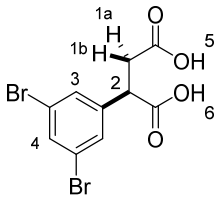
Dimethyl 2-(3,5-dibromophenyl)succinate (413)[167]



A three-necked oven-dried 100 mL round-bottomed flask containing a magnetic stirring bar and equipped with a thermometer was charged with **412** (1.00 g, 2.50 mmol) and conc. HCl (10 mL). Once cooled the mixture to 0°C, a solution of $NaNO_2$ (226 mg, 3.30 mmol) in water (8 mL) was added slowly while keeping the temperature of the reaction mixture below 5 °C. After stirring the resulting mixture at 0 °C for 20 minutes a solution of H_3PO_2 (40 mL, 30% *w*/*v* in water) was added at the same temperature. The reaction was allowed to stir for 2 h at room temperature after which time water (20 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to obtain a yellow oil which was purified by flash column chromatography eluting with 90:10 hexanes:EtOAc to give **413** as a white solid (753 mg, 78%). M.p. 86-87 °C (lit.,[167] m.p. 89-91 °C).

δ_H (400 MHz, $CDCl_3$): 7.58-7.55 (1 H, m, H-4), 7.37-7.35 (2 H, m, H-3), 4.01 (1 H, dd, *J* 5.6, 9.7, H-2), 3.69 (3 H, s, H-6), 3.67 (3 H, s, H-5), 3.13 (1 H, dd, *J* 9.7, 17.0, H-1b) 2.62 (1 H, dd, *J* 5.6, 17.0, H-1a).

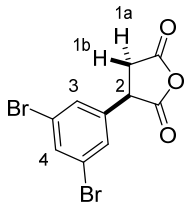
2-(3,5-Dibromophenyl)succinic acid (414)[167]



To a stirred solution of **413** (500 mg, 1.31 mmol) in MeOH (10 mL), was added a 2.0 M aqueous solution of KOH (10 mL). The resulting reaction mixture was heated under reflux for 3 h and then cooled to room temperature. The volatiles were removed under reduced pressure and the pH of the solution was adjusted to = 2 by addition of a 2.0 M aqueous solution of HCl (10 mL). The white precipitate formed was collected by suction filtration and dried *in vacuo* to furnish **414** as a white solid (450 mg, 97%). M.p. 217-220 °C, (lit.,[167] m.p. 227-229 °C).

δ_H (400 MHz, DMSO-d_6): 12.4 (2 H, bs, H-5 and H-6), 7.73 (1 H, d, *J* 1.7, H-4), 7.51 (2 H, d, *J* 1.7, H-3), 3.93 (1 H, dd, *J* 5.6, 9.4, H-2), 2.94 (1 H, dd, *J* 9.4, 16.9, H-1b), 2.61 (1 H, dd, *J* 5.6, 16.9, H-1a).

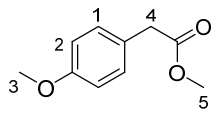
3-(3,5-Dibromophenyl)dihydrofuran-2,5-dione (415)[167]



A 10 mL round-bottomed flask containing a magnetic stirring bar was charged with **414** (300 mg, 0.852 mmol). The apparatus was then fitted with a reflux condenser and freshly distilled acetyl chloride (4 mL) was added *via* syringe under an argon atmosphere. The reaction mixture was heated at 65 °C for 16 h after which time acetyl chloride was then removed *in vacuo* to obtain **415** as a white solid (156 mg, 55%). M.p. 110-112 °C (lit.,[168] m.p. 112-115 °C).

δ_H (400 MHz, DMSO-d_6) 7.80 (1 H, t, *J* 1.7, H-4), 7.75 (2 H, d, *J* 1.7, H-3), 4.67 (1 H, dd, *J* 8.5, 9.9, H-2), 3.48 (1 H, dd, *J* 9.9, 18.4, H-1b), 3.11 (1 H, dd, *J* 8.5, 18.4, H-1a).

Methyl 2-(4-methoxyphenyl)acetate (417)[238]

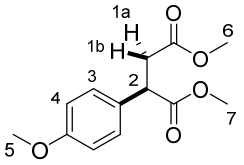


In a 50 mL round-bottomed flask fitted with a condenser and containing a magneting stirring bar, 4-methoxyphenyl acetic acid (**416**, 2.00 g, 12.0 mmol) was dissolved in MeOH (20 mL). Conc. H_2SO_4. was added and the reaction was heated under reflux temperature for 16 h. The reaction mixture was cooled to room temperature, basified by the addition of a 2.0 M aqueous solution of NaOH and extracted with EtOAc (2 x 50 mL). The organic extracts were concentrated, dried over anhydrous $MgSO_4$ and filtered to furnish **417** as a colourless oil (1.79 g, 83%).

δ_H (400 MHz, $CDCl_3$): 7.18 (2 H, d, *J* 8.5, H-1), 6.84 (2 H, d, *J* 8.5, H-2), 3.77 (3 H, s, H-3), 3.66 (3 H, s, H-5), 3.55 (2 H, s, H-4).

HRMS (*m/z* - ESI): $[M]^+$ Found: 180.0782 $C_{10}H_{12}O_3$ Requires: 180.0785.

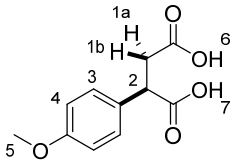
Dimethyl 2-(4-methoxyphenyl)succinate (419)[239]



An oven-dried 50 mL round-bottomed flask containing a magneting stirring bar was charged with freshly distilled diisopropylamine (1.0 mL, 7.20 mmol) and dry THF (3.6 mL) under an argon atmosphere. The solution was cooled to -78 °C and *n*-BuLi (1.6 M in hexanes, 3.7 mL, 5.80 mmol) was added. After 30 min, a solution of **417** (1.04 g, 5.80 mmol) in dry THF (3.0 ml) was added dropwise *via* syringe. After stirring the solution for 45 min, methylbromoacetate (**418**, 597 μL, 9.50 mmol) was added dropwise and the reaction mixture was allowed to stir for 15 min at -78 °C and then for an additional 5 h at room temperature. The reaction was then quenched with a saturated aqueous solution of NH_4Cl (20 mL) and extracted with EtOAc (2 x 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was then purified by flash column chromatography eluting with 70:30 hexanes:EtOAc, to give **419** as a pale yellow solid (695 mg, 45%). M.p. 94-96 °C, (lit.,[239] m.p. 93-94 °C).

δ_H (400 MHz, $CDCl_3$): 7.18 (2 H, d, *J* 8.5, H-3), 6.83 (2 H, d, *J* 8.5, H-4), 4.01 (1 H, dd, *J* 5.4, 9.9, H-2), 3.76 (3 H, s, H-5), 3.64 (3 H, s, H-7), 3.62 (3 H, s, H-6), 3.13 (1 H, dd, *J* 9.9, 16.7, H-1b), 2.62 (1 H, dd, *J* 5.4, 16.7, H-1a).

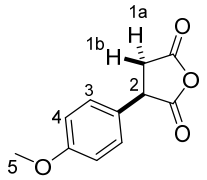
2-(4-Methoxyphenyl)succinic acid (420)[239]



A 100 mL round-bottomed flask equipped with a condenser was charged with **419** (650 mg, 2.40 mmol) followed by a mixture of MeOH (9 mL) and water (6 mL). A 2.0 M aqueous solution of KOH (10 mL) was added and the reaction mixture was heated at reflux temperature for 3 h. The reaction was then cooled to room temperature and MeOH was removed *in vacuo*. The resultant solution was acidified to pH = 2 by the addition of a 2.0 M aqueous solution of HCl (5 mL). The precipitate formed was collected by suction filtration, washed with water (10 mL) and dried *in vacuo* to yield **420** as an off-white solid (495 mg, 91%). M.p. 199-202 °C (lit.[239] m.p. 197-199 °C).

δ_H (400 MHz, DMSO-d_6): 12.25 (2 H, bs, H-6 and H-7), 7.16 (2 H, d, *J* 8.6, H-3), 6.84 (2 H, d, *J* 8.6, H-4), 3.78 (1 H, dd, *J* 5.1, 10.1, H-2), 3.69 (3 H, s, H-5), 2.88 (1 H, dd, *J* 10.1, 16.8, H-1b), 2.55-2.40 (1 H, m, H-1a).

3-(4-Methoxyphenyl)dihydrofuran-2,5-dione (421)[240]

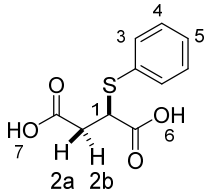


A 25 mL round-bottomed flask equipped with a condenser and containing a magnetic stirring bar was charged with **420** (300 mg, 1.35 mmol) and acetic anhydride (10 mL). The reaction mixture was heated at 80 ºC under an argon atmosphere for 16 h. The volatiles were then removed under reduced pressure to give a yellow oil. Et_2O (4 mL) was added and the mixture was stirred for 1 h at room temperature at 0 °C. The solid

formed was collected by suction filtration, washed with Et_2O (2 x 2 mL) and dried *in vacuo* to furnish **421** as a white solid (137 mg, 50%). M.p. 85-87 °C (lit.[240] m.p. 91-92 °C)

δ_H (400 MHz, DMSO-d_6): 7.30 (2 H, d, *J* 8.6, H-3), 6.89 (2 H, d, *J* 8.6, H-4), 4.51 (1 H, dd, *J* 7.9, 9.8, H-2), 3.71 (3 H, s, H-5), 3.35 (1 H, dd, *J* 9.8, 18.2, H-1b), 3.16 (1 H, dd, *J* 7.9, 18.2, H-1a).

2-(Phenylthio)succinic acid (424)[167]

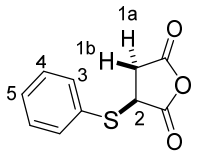


To an oven-dried 100 mL round-bottomed flask equipped with a condenser and containing a magneting stirring bar was added maleic acid (**422**, 2.00 g, 17.2 mmol) followed by anhydrous THF (34.5 mL) and freshly distilled triethylamine (6.0 mL, 43.1 mmol) under an argon atmosphere. Thiophenol (**423**, 1.9 mL, 18.9 mmol) was added *via* syringe and the reaction mixture was heated at reflux temperature for 16 h. The volatiles were removed under reduced pressure and the residue was dissolved in EtOAc (15 mL), then washed with a 2.0 M aqueous solution of NaOH (2 x 15 mL). The aqueous phases were acidified with conc. HCl and the precipitate formed was filtered, washed with Et_2O (2.5 mL) and dried to furnish **424** (3.40 g, 89%) as a white solid. M.p. 89-90 °C. (lit.,[167] m.p. 109-112 °C).

δ_H (400 MHz, DMSO-d_6):* 7.46 (2 H, d, *J* 7.8, H-3), 7.40-7.29 (3 H, m, H-4 and H-5), 3.91 (1 H, dd, *J* 5.3, 9.3, H-1), 2.66 (1 H, dd, *J* 9.3, 16.9, H-2a), 2.62 (1 H, dd, *J* 5.3, 16.9, H-2b).

* The protic signals (H-6 and H-7) are not visible in DMSO-d_6.

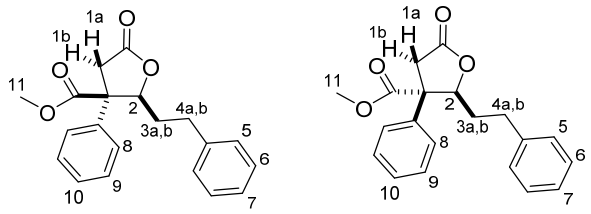
3-(Phenylthio)dihydrofuran-2,5-dione (425)[167]



An oven-dried 50 mL round-bottomed flask fitted with a condenser and containing a magneting stirring bar was charged with **424** (1.00 g, 4.42 mmol) and acetic anhydride (7.5 mL) under an argon atmosphere. The reaction mixture was heated at 90 °C for 2 h, then concentrated in *vacuo* to give a dark brown solid. The crude product was then triturated with Et_2O (5 mL), filtered and dried to give **425** as grey solid (650 mg, 70%). M.p. 35-40 °C.

δ_H (400 MHz, DMSO-d_6): 7.50-7.45 (2 H, m, H-3), 7.40-7.34 (3 H, m, H-4 and H-5), 4.67 (1 H, dd, *J* 5.3, 9.8, H-2), 3.52 (1 H, dd, *J* 9.8, 18.8, H-1b), 2.98 (1 H, dd, *J* 5.3, 18.8, H-1a).

Methyl-5-oxo-2-phenethyl-3-phenyltetrahydrofuran-3-carboxylate (*cis*-**426**, *trans*-**426**, Table 4.7, entry 1)



Prepared according to general procedure H, using freshly distilled hydrocinnamaldehyde (**202**, 32.3 µL, 0.246 mmol) and anhydride **306** (43.3 mg, 0.246 mmol). The reaction was stirred for 15 days to give a diastereomeric mixture of carboxylic acids in a 83:17 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 80:20 hexanes:EtOAc, *cis*-**426** and *trans*-**426** were isolated combined as a white solid (48.7 mg, 61%). M.p 103-105 ºC, TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.85, $[\alpha]_D^{20}$ = +3.7 (*c* = 0.2, $CHCl_3$).* The enantiomeric excesses of *cis*-**426** and *trans*-**426** were found to be 93% and 67% respectively.

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: *cis*-**426** 49.8 min (major enantiomer) and 54.7 min (minor enantiomer); *trans*-**426** 30.0 min (minor enantiomer) and 35.9 min (major enantiomer).

cis-**426**:

δ_H (600 MHz, $CDCl_3$): 7.41-7.30 (5 H, m, H-6, H-9 and H-10), 7.31-7.24 (3 H, m, H-5 and H-7), 7.11-7.05 (2 H, m, H-8), 4.94 (1 H, dd, *J* 1.7, 11.1, H-2), 3.72 (3 H, s, H-11), 3.56 (1 H, d, *J* 17.4, H-1a), 3.14-3.01 (1 H, m, H-4a), 2.93-2.78 (1 H, m, H-4b), 2.79 (1 H, d, *J* 17.4, H-1b), 2.32-2.15 (1 H, m, H-3a), 2.03-1.88 (1 H, m, H-3b).

δ_C (100 MHz, $CDCl_3$): 173.6 (C=O), 171.8 (C=O), 140.3, 138.9, 129.1, 128.7 (C×2), 128.1, 126.7, 125.9, 82.8, 57.8, 53.4, 40.5, 33.7, 32.4.

trans-**426**:

δ_H (600 MHz, $CDCl_3$): 7.41-7.30 (5 H, m, H-6, H-9 and H-10), 7.14-7.16 (3 H, m, H-5 and H-7), 7.14-7.11 (2 H, m, H-8), 5.16 (1 H, dd, *J* 2.0, 11.8, H-2), 3.76 (3 H, s, H-11), 3.33 (1 H, d, *J* 17.3, H-1a), 3.16 (1 H, d, *J* 17.3, H-1b), 2.89-2.78 (1 H, m, H-4a), 2.74-2.63 (1 H, m, H-4b), 1.85-1.70 (1 H, m, H-3a), 1.37-1.24 (1 H, m, H-3b).

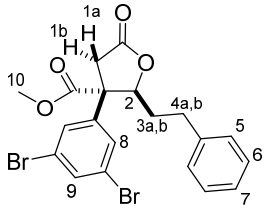
δ_C (100 MHz, $CDCl_3$): 174.9 (C=O), 172.6 (C=O), 139.9, 135.6, 129.0, 128.4, 128.5 (C×2), 126.4, 126.1, 83.8, 57.9, 53.1, 37,4, 32.9, 32.1.

ν_{max} (neat)/cm^{-1}: 2931, 1786, 1735, 1497, 1327, 1291, 1232, 1172, 1033, 951, 747, 695.

HRMS (*m/z* - APCI): $[M+H]^+$ Found:325.1436 $C_{20}H_{21}O_4$ Requires: 325.1434.

*$[\alpha]_D^{20}$ refers to a mixture of *cis*-**426**: *trans*-**426** in a 83:17 ratio

Methyl- 3-(3,5-dibromophenyl)-5-oxo-2-phenethyltetrahydrofuran-3-carboxylate (*trans*-**427**, Table 4.7, entry 2)



Prepared according to general procedure H, using freshly distilled hydrocinnamaldehyde (**202**, 32.3 μL, 0.246 mmol) and anhydride **415** (82.1 mg, 0.246 mmol). The reaction was stirred for 9 days to give a diastereomeric mixture of carboxylic acids in a 8:92 ratio (*cis:trans*). After esterification, *trans*-**427** was isolated and purified by flash column chromatography eluting with 85:15 hexanes:EtOAc to give *trans*-**427** as a yellow oil (96.5 mg, 82%, 92% *ee*). TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.79, $[\alpha]_D^{20}$ = -2.4 (*c* = 0.04, $CHCl_3$).

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 95/5, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: 28.0 (minor enantiomer) and 30.8 (major enantiomer).

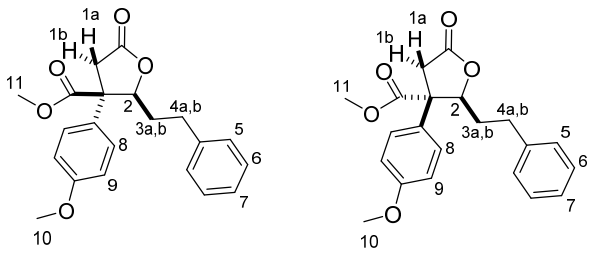
δ_H (600 MHz, $CDCl_3$): 7.62 (1 H, m, H-9), 7.42-7.35 (2 H, m, H-6), 7.32-7.25 (3 H, m, H-5 and H-7), 7.09 (2 H, m, H-8), 4.78 (1 H, dd, *J* 1.6, 11.2, H-2), 3.77 (3 H, s, H-10), 3.45 (1 H, d, *J* 17.1, H-1a), 3.12-3.02 (1 H, m, H-4a), 2.89-2.77 (1 H, m, H-4b), 2.73 (1 H, d, *J* 17.1, H-1b), 2.24-2.11 (1 H, m, H-3a), 1.98-1.88 (1 H, m, H-3b).

δ_C (100 MHz, $CDCl_3$): 172.6 (C=O), 170.8 (C=O), 142.3, 139.7, 133.9, 128.9, 128.6, 128.2, 126.6, 123.6 (C x 2), 81.8, 57.2, 53.2, 40.3, 33.6, 32.1.

ν_{max} (neat)/cm^{-1}: 3027, 2927, 2873, 1785, 1731, 1554, 1411, 1434, 1229, 1166, 1106, 952, 857, 742.

HRMS (*m/z* - APCI): $[M+H]^+$ Found: 480.9624 $C_{20}H_{19}Br_2O_4$ Requires: 480.9644.

Methyl 3-(4-methoxyphenyl)-5-oxo-2-phenethyltetrahydrofuran-3- carboxylate (*cis*-**428**, *trans*-**428**, Table 4.7, entry 3)



Prepared according to general procedure H, using freshly distilled hydrocinnamaldehyde (**202**, 32.3 μL, 0.246 mmol) and anhydride **421** (50.7 mg, 0.246 mmol). The reaction was stirred for 15 days to give a diastereomeric mixture of carboxylic acids in a 80:20 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 85:15 hexanes:EtOAc, *cis*-**428** and *trans*-**428** were isolated combined as a white solid (26.0 mg, 30%). M.p. 92-95 °C. TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.59; $[\alpha]_D^{20}$ = +9.9 (*c* = 0.01, $CHCl_3$).* The enantiomeric excesses of *cis*-**428** and *trans*-**428** were found to be 71% and 61% respectively.

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 95/5, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: *cis*-**428** 40.1 min (minor enantiomer) and 42.9 min (major enantiomer); *trans*-**428** 37.4 min (minor enantiomer) and 51.7 min (major enantiomer).

cis-**428**:

δ_H (400 MHz, $CDCl_3$): 7.38-7.32 (2 H, m, H-5), 7.30-7.25 (3 H, m, H-6 and H-7), 7.01 (2 H, d, *J* 8.8, H-8), 6.85 (2 H, d, *J* 8.8, H-9), 4.88 (1 H, dd, *J* 2.1, 11.7, H-2), 3.81 (3 H, s, H-10), 3.73 (3 H, s, H-11), 3.48 (1 H, d, *J* 17.1, H-1a), 3.11-2.99 (1 H, m, H-4a), 2.88-2.78 (1 H, m, H-4b), 2.79 (1 H, d, *J* 17.1, H-1b), 2.27-2.14 (1 H, m, H-3a), 1.99-1.85 (1 H, m, H-3b).

δ_C (100 MHz, $CDCl_3$): 173.8 (C=O), 172.1 (C=O), 159.1, 140.3, 130.8, 128.7 (C × 2), 127.2, 126.4, 114.4, 83.1, 57.2, 55.3, 52.8, 40.6, 33.7, 32.4.

trans-**428**:

δ_H (400 MHz, $CDCl_3$): 7.23-7.17 (2 H, m, H-5), 7.16-7.11 (3 H, m, H-6 and H-7), 7.08 (2 H, d, *J* 9.2, H-8), 6.89 (2 H, d, *J* 9.2, H-9), 5.13 (1 H, dd, *J* 2.3, 11.2, H-2), 3.82 (3 H, s, H-10), 3.75 (3 H, s, H-11), 3.30 (1 H, d, *J* 17.3, H-1a), 3.12 (1 H, d, *J* 17.3, H-1b), 2.91-2.79 (1 H, m, H-4a), 2.74-2.61 (1 H, m, H-4b), 1.85-1.71 (1 H, m, H-3a), 1.37-1.2 3 (1 H, m, H-3b).

δ_C (100 MHz, $CDCl_3$): 174.2 (C=O), 172.9 (C=O), 159.4, 140.7, 130.8, 128.5, 128.4, 127.9, 126.1, 114.3, 84.0, 57.3, 55.3, 53.1, 37.5, 33.0, 32.1.

ν_{max} (neat)/cm^{-1}: 2922, 1779, 1716, 1512, 1515, 1452, 1340, 1255, 1233, 1205, 1170, 1030, 949. 832, 763, 699, 584.

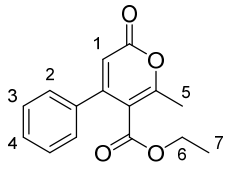
HRMS (*m/z* - ESI): $[M+Na]^+$ Found: 377.1356 $C_{21}H_{22}NaO_5$ Requires: 377.1359.

*$[\alpha]_D^{20}$ refers to a mixture of *cis*-**428**: *trans*-**428** in a 80:20 ratio

General procedure L: Synthesis of anhydride 226, 307 and 437

An oven-dried 25 mL round-bottomed flask containing a magnetic stirring bar under an argon atmosphere was charged with the relevant *bis*-acid precursor (250 mg) of the corresponding anhydride. Freshly distilled acetyl chloride (10 ml) was then added *via* syringe. The flask was fitted with a condenser and the reaction was heated at reflux temperature for 16 h. The mixture was then cooled to room temperature and the solvent was removed *in vacuo* to furnish the crude anhydride that was purified by rapid flash column chromatography eluting with 50:50 hexanes:EtOAc, followed by trituration with Et_2O (3 mL) to afford the desired anhydride.

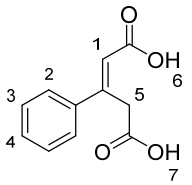
Ethyl 6-methyl-2-oxo-4-phenyl-2*H*-pyran-5-carboxylate (432)[177]



A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with ethyl 3-phenylpropiolate (**430**, 1.4 mL, 8.60 mmol) followed by ethyl 3-oxobutanoate (**431**, 1.0 mL, 8.60 mmol) and 1,4-dioxane (16.5 mL). NaOH (68.8 mg, 1.72 mmol) was added to the solution and the reaction mixture was heated at 90 °C for 16 h. The mixture was then cooled to room temperature, diluted with water (30 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give a pale yellow solid which was purified by trituration with hexanes (5 mL) furnishing **432** as a white solid (1.44 g, 65%). M.p. 84-86 °C, (lit.,[178] m.p. 95-96 °C).

δ_H (400 MHz, $CDCl_3$): 7.44-7.36 (3 H, m, H-2 and H-4), 7.32-7.25 (2 H, m, H-3), 6.14 (1 H, s, H-1), 3.95 (2 H, q, *J* 7.1, H-6), 2.45 (3 H, s, H-5), 0.86 (3 H, t, *J* 7.1, H-7).

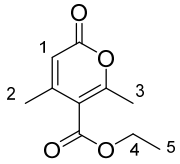
(*E*)-3-Phenylpent-2-enedioic acid (433)[177]



A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with **432** (1.00 g, 3.87 mmol), water (15 mL) and NaOH (760 mg, 19.0 mmol). The flask was fitted with a condenser and the reaction mixture was heated at 80 °C for 5 h. The mixture was then cooled to room temperature and diluted with Et_2O (2 x 10 mL). The pH of the aqueous solution was then adjusted to pH = 2 by the addition of conc. HCl The mixture was then extracted with Et_2O (3 x 10 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated to give a residue that was triturated with Et_2O (3 mL) to afford **433** as a white solid (329 mg, 42%). M.p. 134-136 °C, (lit.[178] m.p. 128-130 °C).

δ_H (400 MHz, DMSO-d_6): 12.36 (2 H, bs, H-6 and H-7), 7.54-7.48 (2 H, m, H-3), 7.45-7.35 (3 H, m, H-2 and H-4), 6.22 (1 H, s, H-1), 4.11 (2 H, s, H-5).

Ethyl 4,6-dimethyl-2-oxo-2*H*-pyran-5-carboxylate (434)[241]



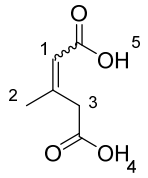
A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with conc. H_2SO_4 (10 mL) and the reaction was cooled to 10 °C. Ethyl 3-oxobutanoate (**431**, 13.0 mL, 102 mmol) was added dropwise *via* syringe while keeping the reaction temperature below 15 °C. The resultant mixture was allowed to stir at room temperature for 72 h after which time the reaction was poured into ice (30 g) and extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with a 10% aqueous solution of

Na_2CO_3 (1 x 50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue obtained was then purified by flash column chromatography eluting with 80:20 hexanes:EtOAc to give **434** as a pale yellow oil (2.86 g, 14%).

δ_H (400 MHz, $CDCl_3$): 6.01 (1 H, s, H-1), 4.32 (2 H, q, *J* 7.0, H-4), 2.40 (3 H, s, H-3), 2.21 (3 H, s, H-2), 1.35 (3 H, t, *J* 7.0, H-5).

HRMS (*m/z* -APCI): $[M-H]^-$ Found: 197.0806 $C_{10}H_{13}O_4$ Requires: 197.0808.

3-Methylpent-2-enedioic acid (**435**)[241]



A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with **434** (1.10 g, 7.60 mmol), water (20 mL) and NaOH (1.52 mg, 38.0 mmol). The flask was fitted with a condenser and the reaction mixture was heated at 80 °C for 5 h. The mixture was then cooled to room temperature and diluted with Et_2O (2 x 10 mL). The pH of the resulting aqueous solution was adjusted to pH = 2 by the addition of conc. HCl. The mixture was then extracted with Et_2O (3 x 10 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and the volatiles were removed to give a residue that was triturated with Et_2O (3 mL) to afford (*E*/*Z*)-**435** in a 72:28 ratio (730 mg, 66%). M.p. 104-107 °C, (lit.,[241] m.p. 101-105 °C).

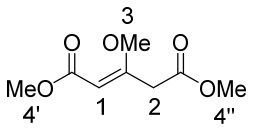
(*E*)-**435**:

δ_H (400 MHz, DMSO-d_6): 12.23 (2 H, bs, H-4 and H-5), 5.70 (1 H, s, H-1), 3.12 (2 H, s, H-3), 2.10 (3 H, s, H-2).

(Z)-**435**:

δ_H (400 MHz, DMSO-d_6): 12.23 (2 H, bs, H-4 and H-5), 5.75 (1 H, s, H-1), 3.63 (2 H, s, H-3), 1.89 (3 H, s, H-2).

(*Z*)-Dimethyl 3-methoxypent-2-enedioate (438)[242]

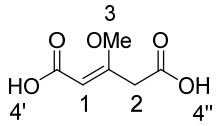


In a 50 mL round-bottomed flask containing a magneting stirring bar, dimethyl-1,3-acetonedicarboxylate (**437**, 1.60 g, 11.5 mmol) was dissolved in MeOH (25 mL). Trimethyl orthoformate (**356**, 2.5 mL, 22.9 mmol) and *p*-toluenesulfonic acid (98.2 mg, 0.57 mmol) were then added. The flask was fitted with a condenser and the reaction mixture was heated at reflux temperature for 3 days under an argon atmosphere. The solvent was then removed *in vacuo* to obtain a yellow oil that was purified by flash column chromatography eluting with 80:20 hexanes: EtOAc, to furnish **438** as a pale yellow oil (875 mg, 40%).

δ_H (400 MHz, $CDCl_3$): 5.19 (1 H, s, H-1), 3.84 (2 H, s, H-2), 3.71 (3 H, s, H-3), 3.69 (3 H, s, H-4'), 3.68 (3 H, s, H-4'').

HRMS (m/z -ESI): $[M+Na]^+$ found 211.0581 $C_8H_{12}O_5Na$ Requires 211.0582.

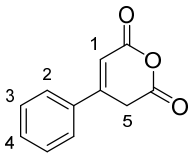
(*Z*)-3-Methoxypent-2-enedioic acid (439)[242]



A 50 mL round-bottomed flask containing a magneting stirring bar was charged with **438** (875 mg, 4.64 mmol) followed by water (14.5 mL) and KOH (1.04 mg, 18.5 mmol). The flask was fitted with a condenser and the reaction mixture was heated at 50 °C for 12 h. The pH of the solution was then adjusted to pH = 2 by the addition of conc. HCl. The mixture was then extracted with Et_2O (3 x 30 mL) and the combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was then triturated with Et_2O (5 mL) to afford **439** as an off white solid (742 mg, 61%). M.p. 177-178 °C, (lit.,[242] 180-182 °C).

δ_H (400 MHz, DMSO-d_6): 12.05 (2 H, s, H-4' and H-4''), 5.12 (1 H, s, H-1), 3.68 (2 H, s, H-2), 3.61 (3 H, s, H-3).

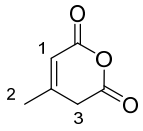
Phenyl-2*H*-pyran-2,6(3*H*)-dione (226)[243]



Synthesised according to general procedure L, using **433** as *bis*-acid precursor (250 mg, 1.21 mmol). After purification, **226** was obtained as a white solid (118 mg, 51%). M.p. 195-197 °C, (lit.,[243] m.p. 193-195 °C).

δ_H (400 MHz, DMSO-d_6): 7.79 (2 H, d, *J* 6.7, H-2), 7.55-7.41 (3 H, m, H-3 and H-4), 6.78 (1 H, s, H-1), 4.15 (2 H, s, H-5).

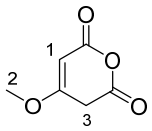
4-Methyl-2*H*-pyran-2,6(3*H*)-dione (436)[241]



Synthesised according to general procedure L, using **435** as *bis*-acid precursor (250 mg, 1.73 mmol). After purification, **436** was obtained as a white solid (116 mg, 36%). M.p. 73-75 °C, (lit.,[243] m.p. 79-83 °C).

δ_H (400 MHz, DMSO-d_6): 6.09 (1 H, s, H-1), 3.64 (2 H, s, H-3), 1.97 (3 H, s, H-2).

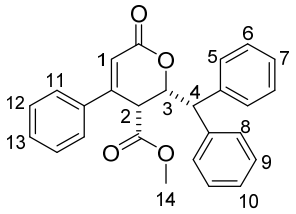
4-Methoxy-2H-pyran-2,6(3H)-dione (307)[242]



Synthesised according to general procedure L, using **439** as *bis*-acid precursor (250 mg, 1.56 mmol). After purification, **307** was obtained as a white solid (77.5 mg, 35%). M.p. 84-86 °C, (lit.,[242] 85-87 °C).

δ_H (400 MHz,DMSO-d_6): 5.55 (1 H, s, H-1), 3.78 (3 H, s, H-2), 3.72 (2 H, s, H-3).

Methyl 2-benzhydryl-6-oxo-4-phenyl-3,6-dihydro-2H-pyran-3-carboxylate (*cis*-**442**, Scheme 4.17)



Prepared according to general procedure I, using freshly distilled diphenylacetaldehyde (**440**, 43.6 μL, 0.246 mmol). The reaction was stirred for 2 days furnishing only the diastereomer *cis*-**442**. Upon esterification, the reaction gave a diastereomeric mixture of esters in a 90:10 ratio (*trans*:*cis*). The major diastereomer *cis*-**442** was then isolated by flash column chromatography, eluting with 95:5 hexanes:EtOAc, as a white solid (96.1 mg, 98%, 99% *ee*). M.p. 142-144 °C, TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.67, $[\alpha]_D^{20}$ = -2.8 (*c* = 0.04, $CHCl_3$).

CSP-HPLC analysis. ACQUITY UPC^2, Trefoil AMY1, 2.5μm (3.0 x 150mm). ABPR: 1500 (psi). A (CO_2) = 97%/B (Ethanol/CAN/IPA 1:1:1, *v:v*) = 3%, 1.2 mL min^{-1}, 30 °C, UV detection at 254 nm, retention times: 2.9 min.

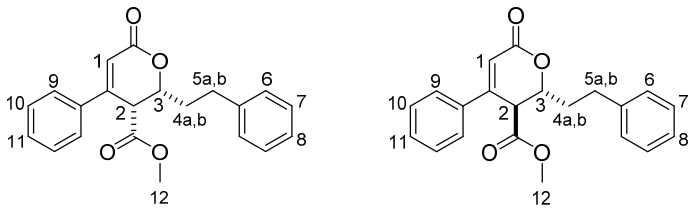
δ_H (400 MHz, $CDCl_3$): 7.49-7.45 (2 H, m, H-11), 7.44-7.39 (5 H, m, H-5, H-12 and H-13),7.38-7.35 (4 H, m, H-8 and H-9),7.35-7.29 (3 H, m, H-6 and H-10), 7.21- 7.19 (1 H, m, H-7) ,6.55 (1 H, s, H-1), 5.37 (1 H, dd, *J* 1.4, 10.6, H-3), 4.33 (1 H, d, *J* 10.6, H-4), 3.82 (1 H, d, *J* 1.4, H-2), 3.67 (3 H, s, H-14).

δ_C (100 MHz, $CDCl_3$): 168.1 (C=O), 164.4 (C=O), 152.3, 140.2, 139.9, 134.6, 130.9, 129.2, 129.1, 128.6, 128.2, 128.23, 127.5, 126.9, 126.3, 116.7, 79.7, 53.7, 52.8, 44.9.

ν_{max} (neat)/cm^{-1}: 3088, 2971, 2923, 1660, 1592, 1506, 1472, 1311, 1217, 1072, 998, 768, 642.

HRMS (m/z -ESI): $[M+Na]^+$ Found: 421.1407 $C_{26}H_{22}O_4Na$ Requires: 421.1410.

Methyl 6-oxo-2-phenethyl-4-phenyl-3,6-dihydro-2H-pyran-3-carboxylate (*cis*-**445**, *trans*-**445**, Table 4.9, entry 3)



Prepared according to general procedure I, freshly distilled hydrocinnamaldehyde (**202**, 32.4 µL, 0.246 mmol). The reaction was stirred for 18 hours to give a diastereomeric mixture of carboxylic acids in a 86:14 ratio (*cis:trans*). After purification by flash column chromatography, eluting with 75:25 hexanes:EtOAc, *cis*-**445** and *trans*-**445** were isolated combined as a pale yellow oil (52.9 mg, 64%). TLC (hexanes/EtOAc, 8:2 *v/v*): $R_f = 0.63$, $[\alpha]_D^{20} = -8.9$ (*c* = 0.5, $CHCl_3$).* The enantiomeric excesses of *cis*-**445** and *trans*-**445** were found to be 76% and 45% respectively.

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: *cis*-**445** 17.6 min (major enantiomer) and 23.3 min (minor enantiomer); *trans*-**445** 15.0 min (major enantiomer) and 21.7 min (minor enantiomer).

cis-**445**:

δ_H (400 MHz, $CDCl_3$): 7.56-7.52 (2 H, m, H-9), 7.48-7.42 (3 H, m, H-10 and H-11), 7.35-7.30 (2 H, m, H-6), 7.27-7.20 (3 H, m, H-7 and H-8), 6.54 (1 H, s, H-1), 4.61-4.53 (1 H, m, H-3), 3.77 (1 H, d, *J* 3.5, H-2), 3.74 (3 H, s, H-12), 3.06-2.94 (1 H, m, H-5a), 2.94-2.83 (1 H, m, H-5b), 2.25-2.14 (1 H, m, H-4a), 2.13- 2.03 (1 H, m, H-4b).

δ_C (100 MHz, $CDCl_3$): 168.4 (C=O), 164.6 (C=O), 151.6, 140.4, 134.6, 131.0, 129.2, 128.7, 128.6, 126.3, 126.0, 116.6, 67.9, 52.9, 47.0, 34.2, 31.2.

trans-**445**:

δ_H (400 MHz, $CDCl_3$): 7.56-7.52 (2 H, m, H-9), 7.48-7.42 (3 H, m, H-10 and H-11), 7.35-7.30 (2 H, m, H-6), 7.27-7.20 (3 H, m, H-7 and H-8), 6.43 (1 H, s, H-1), 4.96-4.90 (1 H, m, H-3), 3.83 (1 H, d, *J* 4.0, H-2), 3.65 (3 H, s, H-12), 2.97-2.93 (1 H, m, H-5a), 2.84-2.77 (1 H, m, H-5b), 2.30-2.22 (1 H, m, H-4a), 2.02-1.93(1 H, m, H-4b).

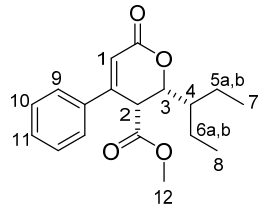
δ_C (100 MHz, $CDCl_3$): 169.9 (C=O), 163.0 (C=O), 151.7, 140.3, 134.7, 130.6, 129.2, 128.8, 128.5, 126.6, 126.1, 116.9, 78.5, 52.9, 47.3, 35.6, 31.6.

ν_{max} (neat)/cm^{-1}: 2925, 2856, 1725, 1458, 1261, 1239, 1158, 1112, 1086, 1030, 993, 709, 645.

HRMS (*m/z* - ESI): $[M+H]^+$ Found: 337.1443 $C_{21}H_{21}O_4$ Requires: 337.1434.

*$[\alpha]_D^{20}$ refers to a mixture of *cis*-**445**: *trans*-**445** in a 86:14 ratio

Methyl 6-oxo-2-(pentan-3-yl)-4-phenyl-3,6-dihydro-2H-pyran-3-carboxylate (*cis*-**447**, Table 4.10, entry 1)



Prepared according to general procedure I, using freshly distilled 2-ethylbutyraldehyde (**403**, 30.3 μL, 0.246 mmol). The reaction was stirred for 72 hours to give a diastereomeric mixture of carboxylic acids in a 95:5 ratio (*cis:trans*). After esterification and purification by flash column chromatography, eluting with 80:20 hexanes:EtOAc, *cis*-**447** was isolated as a white solid (41.6 mg, 56%, 99% *ee*). M.p. 132-134 °C, TLC (hexanes/EtOAc, 8:2 *v/v*): $R_f = 0.5$, $[\alpha]_D^{20} = -3.6$ (*c* = 0.04, $CHCl_3$).

CSP-HPLC analysis. Chiralcel OD (4.6 mm x 25 cm), hexane/IPA: 90/10, 0.3 mL min^{-1}, RT, UV detection at 254 nm, retention times: 55.7 min.

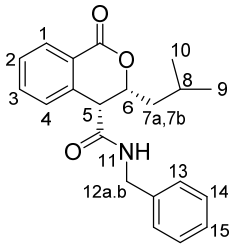
δ_H (400 MHz, $CDCl_3$): 7.63-7.54 (2 H, m, H-10), 7.48-7.44 (3 H, m, H-9 and H-11), 6.55 (1 H, s, H-1), 4.44 (1 H, dd, *J* 3.1, 9.1, H-3), 3.93 (1 H, d, *J* 3.1, H-2), 3.73 (3 H, s, H-12), 1.84-1.69 (3 H, m, H-4, H-5a, H-6a), 1.70-1.62 (1 H, m, H-5b), 1.53-1.44 (1 H, m, H-6b), 0.98-0.94 (6 H, m, H-7 and H-8).

δc (100 MHz, $CDCl_3$): 168.7 (C=O), 165.0 (C=O), 152.1, 134.9, 130.9, 129.2, 126.2, 116.8, 79.9, 52.9, 45.2, 41.7, 20.2, 19.7, 9.9, 9.6.

ν_{max} (neat)/cm^{-1}: 3086, 2965, 2877, 1721, 1696, 1624, 1446, 1353, 1269, 1245, 1086, 1012, 990, 893, 777, 689, 602, 576.

HRMS (*m/z* -APCI): $[M+H]^+$ Found: 303.1598 $C_{18}H_{23}O_4$ Requires: 303.1590.

(3*R*,4*R*)-*N*-benzyl-3-isobutyl-1-oxoisochromane-4-carboxamide (*cis*-**453**, Table 4.10, entry 5)



Prepared according to general procedure K, using anhydride **147** (39.9 mg, 0.246 mmol) and freshly distilled isovaleraldehyde (27.0 µL, 0.246 mmol). The reaction was stirred at -15 °C for 48 h to give a diastereomeric mixture of carboxylic acids in a 78:22 ratio (*cis:trans*). After amidation, the crude mixture of diastereomeric carboxamide lactones was purified by flash column chromatography eluting with 70:30 hexanes:EtOAc to give *cis*-**453** as a white solid (58.9 mg, 70%, 99% *ee*). M.p. 148-150 ºC, TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.3, $[\alpha]_D^{20}$ = -4.1 (*c* = 0.03 , $CHCl_3$).

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 33.6 min.

δ_H (600 MHz, $CDCl_3$): 8.19 (1 H, d, *J* 7.8, H-1), 7.64 (1 H, app.t, *J* 7.8, H-2), 7.52 (1 H, app.t, *J* 7.8, H-3), 7.43 (1 H, d, *J* 7.8, H-4), 7.34-7.21 (3 H, m, H-14 and H-15), 7.15 (2 H, d, *J* 7.2, H-13), 5.90 (1 H,

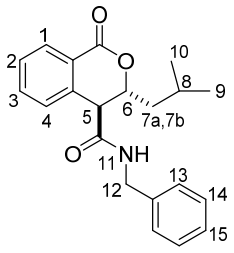
bs, H-11), 4.79 (1 H, ddd, *J* 3.3, 4.5, 9.2, H-6), 4.45 (1 H, dd, *J* 5.9, 15.1, H-12a), 4.35 (1 H, dd, *J* 5.6, 15.1, H-12b), 3.77 (1 H, d, *J* 3.3, H-5), 2.01-1.88 (1 H, m, H-8), 1.99 (1 H, ddd, *J* 5.9, 9.2, 14.6, H-7a), 1.66 (1 H, ddd, *J* 4.5, 8.4, 14.6, H-7b), 1.00-0.93 (6 H, m, H-9 and H-10).

δ_C (100 MHz, $CDCl_3$): 168.0 (C=O), 164.9 (C=O), 138.1, 137.6, 134.4, 131.1, 129.1, 128.7, 127.8, 127.5, 127.4, 124.5, 77.8, 49.9, 43.7, 33.8, 24.9, 22.9, 21.9.

ν_{max} (neat)/cm^{-1}: 3318, 2955, 1712, 1641, 1609, 1459, 1288, 1235, 1089, 1036, 740, 701.

HRMS (*m/z* - ESI): $[M+H]^+$ Found: 338.1746 $C_{21}H_{24}NO_3$ Requires: 338.1750

N-benzyl-3-isobutyl-1-oxoisochromane-4-carboxamide (*trans*-**453**, Table 4.10, entry 5)



Prepared according to general procedure K, using anhydride **147** (39.9 mg, 0.246 mmol) and freshly distilled isovaleraldehyde (27.0 μL, 0.246 mmol). The reaction was stirred at -15 °C for 48 h to give a diastereomeric mixture of carboxylic acids in a 78:22 ratio (*cis:trans*). After amidation, the crude mixture of diastereomeric carboxamide lactones was purified by flash column chromatography eluting with 65:35 hexanes:EtOAc to give *trans*-**453** as a white solid (16.6 mg, 21%, 91% *ee*) M.p. 148-150 ºC, (hexanes/EtOAc, 8:2 *v/v*): $R_f = 0.5$ $[\alpha]_D^{20} = +0.7$ (*c* = 0.03, $CHCl_3$).

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 221 nm, retention times: 16.3 (minor enantiomer) and 21.9 min (major enantiomer).

δ_H (600 MHz, $CDCl_3$): 8.16 (1 H, d, *J* 7.7, H-1), 7.62 (1 H, app. t, *J* 7.7, H-2), 7.50 (1 H, app. t, *J* 7.7, H-3), 7.37-7.29 (4 H, m, H-4, H-14 and H-

15), 7.22 (2 H, d, *J* 7.2, H-13), 5.89 (1 H, bs, H-11), 5.14 (1 H, ddd, *J* 4.3, 5.2, 9.7, H-6), 4.49 (2 H, d, *J* 5.9, H-12), 3.67 (1 H, d, *J* 5.2, H-5), 2.01-1.89 (1 H, m, H-8), 1.71 (1 H, ddd, *J* 4.9, 9.7, 13.9, H-7a), 1.37 (1 H, ddd, *J* 4.3, 8.9, 13.9, H-7b), 0.98-0.92 (6 H, m, H-9 and H-10).

δ_C (100 MHz, $CDCl_3$): 169.5 (C=O), 163.7 (C=O), 137.4, 136.3, 134.5, 130.1, 129.0, 128.8, 127.9, 127.7, 127.5, 124.9, 78.5, 50.4, 44.0, 42.7, 24.4, 23.1, 21.6.

ν_{max} (neat)/cm^{-1}: 3304, 2948, 1726, 1521, 1457, 1256, 1110, 1024, 691, 562.

HRMS (*m/z* - APCI): $[M+H]^+$ Found: 338.1754 $C_{21}H_{24}NO_3$ Requires 338.1750

6.5 Experimental procedure and data for Chapter 5

General procedure M: racemic preparation of compounds 473, 477, 480 and 481 (Tables 5.1-5.8)

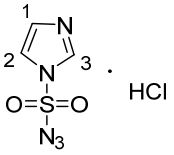
An oven-dried 10 mL round-bottomed flask containing a magnetic stirring bar under an argon atmosphere was charged with the relevant anhydride (1.0 equiv.). Anhydrous THF (0.1 M, 2.5 mL) was added *via* syringe and the relevant aldehyde (1.0 equiv.) followed by catalyst **459** or **464** (5 mol%) were added to the reaction mixture which was allowed to stir at room temperature for 16 h. Anhydrous isopropyl alcohol (94 μL, 1.23 mmol) and trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 150 μL, 0.300 mmol) were added *via* syringe at -15 °C and the reaction was allowed to stir for 15 min at the same temperature. The crude reaction mixture containing the diastereomeric esters was then directly loaded into the silica column and the two diastereomers were isolated.

General procedure N: enantioselective preparation of compounds 442, 447, 477, 480 and 481 (Scheme 5.5, Tables 5.5-5.7)

An oven-dried 10 mL round-bottomed flask containing a magnetic stirring bar under an argon atmosphere was charged with phenyl glutaconic anhydride (**226**, 46.3 mg, 0.246 mmol). Anhydrous THF or MTBE (0.1 M, 2.5 mL) was added *via* syringe and the relevant aldehyde (1.0 equiv.) followed by catalyst **304** or **474** (5 mol%) were added to the reaction mixture which was allowed to stir at room temperature for a time indicated in the relative

Table. Anhydrous isopropyl alcohol (94 µL, 1.23 mmol) and trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 150 µL, 0.300 mmol) were added *via* syringe at -15 °C and the reaction was allowed to stir for 15 min at the same temperature. The crude reaction mixture containing the diastereomeric esters was then directly loaded into the silica column and purified to furnish the two diastereomers - the enantiomeric excesses of which were determined by CSP-HPLC.

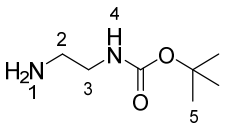
1H-imidazole-1-sulfonyl azide hydrogen chloride (456)[244]



A 250 mL round-bottomed flask containing a magnetic stirring bar was charged with NaN_3 (**460**, 5.00 g, 77.0 mmol) and CH_3CN (77 mL). Sulfuryl chloride (6.2 mL, 77.0 mmol) was added dropwise *via* syringe at 0° C and the reaction mixture was allowed to stir for 16 h at room temperature. Imidazole (10.0 g, 146 mmol) was then added portionwise to the ice-cooled solution and the resulting mixture stirred for 3 h at room temperature. The reaction was diluted with EtOAc (100 mL), washed with H_2O (2 x 100 mL) followed by a saturated aqueous solution of $NaHCO_3$ (2 x 100 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and filtered. To the stirred filtrate was added a solution of HCl in EtOH (8.20 mL, 115 mmol) dropwise at 0°C, and the resulting suspension was then filtered. The solid obtained was then washed with EtOAc (3 x 100 mL) to furnish **456** as colourless needles (3.50 g, 22%). M.p.100-101°C, (lit.,[245] m.p. 100-102 °C).

δ_H (400 MHz, D_2O): 9.12 (1 H, dd, *J* 1.3, 1.6, H-3), 7.85 (1 H, dd, *J* 1.6, 2.2, H-1), 7.43 (1 H, dd, *J* 1.3, 2.2, H-2).

***tert*-butyl (2-aminoethyl)carbamate (455)**[245]



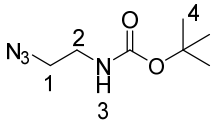
A 500 mL round-bottomed flask containing a magnetic stirring bar was charged with ethylenediamine (**454**, 5.6 mL, 83.3 mmol) and CH_2Cl_2 (25 mL). A solution of di-*tert*-

butyl dicarbonate (3.0 g, 14.0 mmol) in CH_2Cl_2 (200 mL) was then added dropwise over 3 h and the reaction mixture was allowed to stir for 12 h at room temperature. The volatiles were then removed under reduced pressure and the oil obtained was dissolved in a saturated aqueous solution of Na_2CO_3 (300 mL) and extracted with CH_2Cl_2 (2 x 150 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield **455** as colourless oil (1.60 g, 71%).

δ_H (400 MHz, $CDCl_3$): 4.90 (1 H, bs, H-4), 3.13 (2 H, m, H-3), 2.76 (2 H, m, H-2), 1.41 (9 H, s, H-5), 1.22 (2 H, bs, H-1).

HRMS (*m/z* - APCI): $[M+H]^+$ Found: 161.1289 $C_7H_{17}N_2O_2$ Requires: 161.1284.

***tert*-butyl (2-azidoethyl)carbamate (457)**[246]

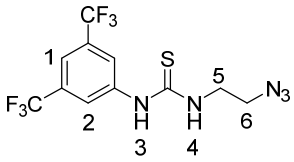


To a stirred suspension of **455** (1.60 g, 9.98 mmol), K_2CO_3 (2.35 g, 16.9 mmol) and $CuSO_4 \cdot 5H_2O$ (24.9 mg, 0.10 mmol) in MeOH (50 ml) was added **456** (2.50 g, 11.9 mmol) portionwise at 0°C behind a blast-shield. The resultant reaction mixture was allowed to stir for 14 h and the solvent was removed under a steam of N_2. The reaction mixture was diluted with H_2O (25 mL) and Et_2O (25 mL). The aqueous layers were extracted with Et_2O and the combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was then purified by flash column chromatography, eluting with 80:20 hexanes:EtOAc, to afford **457** as a colourless oil (1.27g, 68%).

δ_H (400 MHz, $CDCl_3$): 4.81 (1 H, bs, H-3), 3.39 (2 H, m, H-2), 3.27 (2 H, m, H-1), 1.43 (9 H, s, H-4).

HRMS (*m/z* – APCI-DIP): $[M-H]^-$ Found: 185.1048 $C_7H_{13}N_4O_2$ Requires: 185.1044.

1-(2-azidoethyl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea (458)



A 25 mL round-bottomed flask containing a magnetic stirring bar was charged with **457** (963 mg, 5.17 mmol) followed by 1,4-dioxane (10.3 mL). A solution of HCl (4.0 N in 1,4-dioxane, 2.1 mL) was added at 0° C and the reaction mixture was allowed to stir at room temperature for 48 h. The volatiles were then removed under N_2 steam and the precipitated formed was filtered, washed with EtOAc (5 mL) and dried. The crude aminoazide was then dissolved in dry THF (2.4 mL) and 3,5-*bis*(trifluoromethyl)phenyl isothiocyanate (944 μL, 5.17 mmol) was added dropwise *via* syringe. The reaction mixture was stirred at room temperature for 12 h. The solvent was then removed under reduced pressure and the crude product was purified by flash column chromatography, eluting with 85:15 hexanes:EtOAc, to give **458** as a colourless solid (474 mg, 56% over 2 steps). M.p: 73-75 °C, TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.57.

δ_H (400 MHz, $CDCl_3$): 7.89 (1 H, bs, H-3), 7.82 (1 H, s, H-1), 7.78 (2 H, s, H-2), 6.39 (1 H, bs, H-4), 3.87 (2 H, m, H-5), 3.70 (2 H, t, *J* 5.8, H-6).

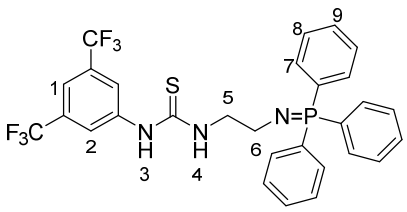
δ_C (100 MHz, $CDCl_3$): 181.1, 138.6, 133.2 (q, J_{CF} 34.2), 122.7 (q, J_{CF} 270.7), 124.0, 120.0, 50.3, 44.2.

δ_F (400 MHz, $CDCl_3$): -63.0.

ν_{max} (neat)/cm^{-1}: 3233, 3035, 2115, 1535, 1470, 1379, 1335, 1122, 1269, 1175, 991, 892, 703, 646.

HRMS (*m/z* - APCI): $[M+H]^+$ Found: 358.0555 $C_{11}H_{10}F_6N_5S$ Requires: 358.0549.

1-(3,5-bis(trifluoromethyl)phenyl)-3-(2-((triphenyl-l5-phosphaneylidene)amino)ethyl)thiourea (**459**)



In a 25 mL round-bottomed flask containing a magnetic stirring bar **458** (412 mg, 1.15 mmol) was dissolved in Et_2O (2.9 mL). Triphenylphosphine (302 mg, 1.15 mmol) was added at room temperature under an argon atmosphere and the reaction mixture was

allowed to stir for 26 h. Pentane (2 mL) was then added *via* syringe and the resulting suspension was stirred vigorously for 2 h. The precipitated formed was then filtered, washed and dried *in vacuo* to afford **459** as an off white solid (251 mg, 37%). M.p 77-80 °C.

δ_H (400 MHz, $CDCl_3$):* 7.72-7.64 (3 H, m, H-1, H-2), 7.62-7.51 (9 H, m, H-8 and H-9), 7.51-7.39 (6 H, m, H-7), 3.69-3.57 (2 H, m, H-5), 3.31-3.18 (2 H, m, H-6).

δ_C (100 MHz, $CDCl_3$): 181.1, 143.2, 132.1 (d, J_{CP} 9.8), 130.9 (q, J_{CF} 30.6), 128.9, 128.6 (d, J_{CP} 12.1), 128.0, 124.1, 123.1 (q, J_{CF} 271.3), 117.1, 50.5-49.8 (m), 47.9-47.5 (m)

δ_F (376.5 MHz, $CDCl_3$): -62.8.

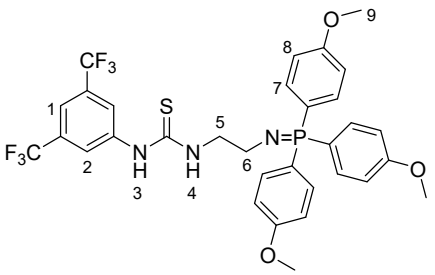
δ_P (202 MHz, $CDCl_3$): 29.3.

ν_{max} (neat)/cm^{-1}: 3216, 2817, 1589, 1468, 1438, 1378, 1273, 1168, 1117, 997, 885, 715, 692, 680.

HRMS (*m/z* - ESI): $[M+H]^+$ Found: 592.1411 $C_{29}H_{25}F_6N_3PS$ Requires: 592.1405.

* The protic signals (H-3 and H-4) are not visible in $CHCl_3$

1-(3,5-bis(trifluoromethyl)phenyl)-3-(2-(4-methoxy(triphenyl-l5-phosphaneylidene)amino)ethyl)thiourea (**464**)



To a 25 mL round-bottomed flask containing a magnetic stirring bar was added **458** (128 mg, 0.36 mmol), followed by Et_2O (1 mL) and tris(4-methoxyphenyl)phosphine (**463**, 126.7 mg, 0.36 mmol) under an argon atmosphere. The reaction mixture was allowed to stir at room temperature for 12 h, after which time pentane (1 mL) was added and the resultant suspension was stirred vigorously for 2 h. The solid formed was filtered, washed

with pentane:Et_2O (1:1) and dried *in vacuo* to give **464** as off white solid (98.1 mg, 40%). M.p. 84-87 °C.

δ_H (400 MHz, $CDCl_3$):* 7.57 (2 H, bs, H-2), 7.52-7.42 (6 H, m, H-7), 7.31 (1 H, bs, H-1), 7.04-6.94 (6 H, m, H-8), 3.87 (9 H, s, H-9), 3.71-3.61 (2 H, m, H-5), 3.15-3.06 (2 H, m, H-6).

δ_C (100 MHz, $CDCl_3$): 181.6, 163.7, 162.4, 134.7 (d, J_{CP} 11.6), 133.7, 130.6 (q, J_{CF} 32.0), 124.1, 123.6 (q, J_{CF} 273.4), 116.3, 115.0 (d, J_{CP} 13.6), 65.8, 55.3, 47.6-46.1 (m).

δ_F (400 MHz, $CDCl_3$): -62.6

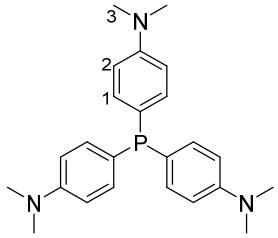
δ_P (202 MHz, $CDCl_3$): 26.5

ν_{max} (neat)/cm^{-1}: 2981, 1597, 1557, 1502, 1382, 1272, 1163, 1110, 803, 827.

HRMS (*m/z* - ESI): $[M+H]^+$ Found: 682.1715 $C_{32}H_{31}F_6N_3O_3PS$ Requires: 682.1722.

* The protic signals (H-3 and H-4) are not visible in $CHCl_3$

Tris(*p*-dimethylaminophenyl)phosphine (466)[247]



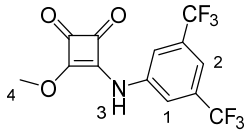
A 100 mL three-necked round-bottomed flask equipped with a condenser and containing a magnetic stirring bar under an argon atmosphere was charged with magnesium turnings (90.0 mg, 3.70 mmol), LiCl (106 mg, 2.50 mmol) and dry THF (1.7 mL). A solution of 4-bromo-*N*,*N*-dimethylaniline (**465**, 500 mg, 2.50 mmol) in dry THF (700 µL) was then added and the reaction mixture was heated at 40 °C and stirred vigorously. A reminder solution of 4-bromo-*N*,*N*-dimethylaniline(500 mg, 2.50 mmol) in dry THF (700 µL) was then added. After stirring the reaction for 1 h at room temperature, the mixture was cooled to 0 °C and PBr_3 (71 µL, 0.75 mmol) was added dropwise. The resulting mixture was allowed to stir for 20 min at room temperature and then quenched with a saturated solution

of NH_4Cl at 0 °C. The aqueous layers were extracted with $CHCl_3$, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue obtained was then purified by trituration with hexanes to furnish **466** as an ocher solid (176 mg, 18%). M.p. 205-206 °C (lit.[248], m.p. 206-207 °C)

δ_H (600 MHz, $CDCl_3$): 7.48-7.36 (6 H, m, H-1), 6.66 (6 H, d, *J* 8.2, H-2), 2.96 (18 H, s, H-3).

δ_P (202 MHz, $CDCl_3$): -10.7.

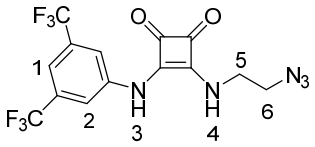
3-((3,5-*bis*(Trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (468)[249]



A 50 mL round-bottomed flask containing a magnetic stirring bar under an argon atmosphere was charged with **356** (400 mg, 2.81 mmol), dry MeOH (8 mL) and 3,5-*bis*-(trifluoromethyl)aniline (438 μL, 2.81 mmol). The reaction mixture was allowed to stir at room temperature for 3 days. The volatiles were removed under reduced pressure and the residue was purified by flash column chromatography, eluting with 70:30 hexanes:EtOAc, to afford **468** as a white solid (776 mg, 60%). M.p. 192-194 °C (lit.,[248] m.p. 179-181 °C), TLC (hexanes:EtOAc, 2:1 *v/v*): R_f = 0.28.

δ_H (400 MHz, DMSO-d_6): 11.19 (1 H, s, H-3), 8.03 (2 H, s, H-1), 7.69 (1 H, s, H-2), 4.40 (3 H, s, H-4).

3-((2-azidoethyl)amino)-4-((3,5-bis(trifluoromethyl)phenyl)amino)cyclobut-3-ene-1,2-dione (469)



A 25 mL round-bottomed flask containing a magnetic stirring bar was charged with **457** (963 mg, 5.20 mmol) followed by 1,4-dioxane (10.3 mL). A solution of HCl (4 N in 1,4-dioxane, 2.1 mL) was added at 0° C and the reaction mixture was allowed to stir at room

temperature for 48 h. The solvent was then removed under N_2 steam and the solid obtained was filtered, washed with EtOAc (5 mL) and dried. The crude aminoazide was then dissolved in THF (6.8 mL) and **458** (512 mg, 5.2 mmol) was added portionwise. The reaction mixture was stirred at room temperature for 48 h. The solvent was then removed *in vacuo* and the crude product was purified by flash column chromatography, eluting with 40:60 hexanes:EtOAc, to give **469** as a white solid (112 mg, 6%). M.p: 73-75 °C, TLC (hexanes/EtOAc, 6:4 *v/v*): R_f = 0.57

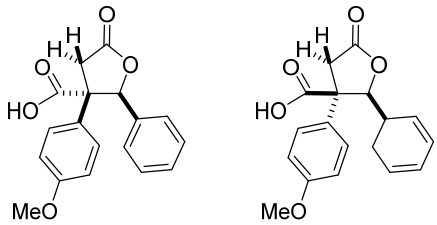
δ_H (600 MHz, $CDCl_3$): 10.30 (1 H, bs, H-3), 8.03 (1 H, s, H-1), 7.88 (1 H, bs, H-4), 7.67 (2 H, s, H-2), 3.85-3.76 (2 H, m, H-5), 3.64- 3.57 (2 H, m, H-6).

δ_C (100 MHz, $CDCl_3$): 185.1 (C=O), 181.2 (C=O), 171.5, 170.3, 141.5, 131.7 (q, J_{CF} 34.1), 123.5 (q, J_{CF} 273.5), 118.5, 115.3, 51.7, 43.7.

ν_{max} (neat)/cm^{-1}: 3210, 3092, 2100, 1768, 1665, 1586, 1569, 1445, 1375, 1340, 1276, 1171, 934, 878, 905, 721, 678.

HRMS (*m/z* - ESI): $[M+Na]^+$ Found: 416.0549 $C_{14}H_9F_6N_5O_2Na$ Requires: 416.0552.

3-(4-Methoxyphenyl)-5-oxo-2- phenyltetrahydrofuran-3-carboxylic acid (*trans*-**461**, *cis*-**461**, Table 5.1, entry 4)

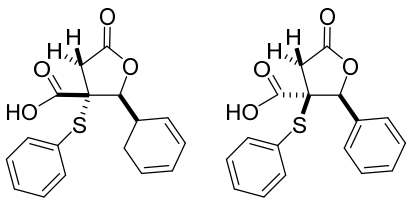


Synthesised according to general procedure M, using anhydrous THF (0.1 M, 2.5 mL), freshly distilled benzaldehyde (**135**, 25.0 μL, 0.246 mmol) anhydride **421** (50.7 mg, 0.246 mmol) and catalyst **459** (7.30 mg, 0.0123 mmol - 5 mol%). The reaction was stirred for 32 h to give a diastereomeric mixture of carboxylic acids in a 73:27 ratio (*trans:cis*) in 13% yield which was monitored by using *p*-iodoanisole (28.8 mg, 0.123 mmol).

Due to the low conversion of the reaction, esterification was not carried out and *trans*-**461** and *cis*-**461** were not isolated.

(See Appendix for ^{1}H NMR spectroscopic analysis).

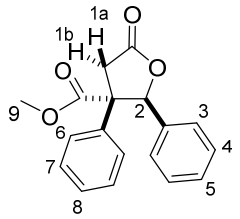
5-oxo-2-phenyl-3-(phenylthio)tetrahydrofuran-3-carboxylic acid (*trans*-**462**, *cis*-**462**, Table 5.3, entry 2)



Synthesised according to general procedure M, using anhydrous THF (0.1 M, 2.5 mL), freshly distilled benzaldehyde (**135**, 25.0 µL, 0.246 mmol) anhydride **425** (51.2 mg, 0.246 mmol) and catalyst **464** (8.38 mg, 0.0123 mmol - 5 mol%). The reaction was stirred for 32 h to give a diastereomeric mixture of carboxylic acids in a 75:25 ratio (*trans:cis*) in 12% yield which was monitored by ^{1}H NMR spectroscopic analysis using *p*-iodoanisole (28.8 mg, 0.123 mmol). Due to the low conversion of the reaction, esterification was not carried out and *trans*-**462** and *cis*-**462** were not isolated.

(See Appendix for ^{1}H NMR spectroscopic analysis).

Methyl 5-oxo-2,3-diphenyltetrahydrofuran-3-carboxylic acid (*trans*-**473**, Table 5.4, entry 4)[167]

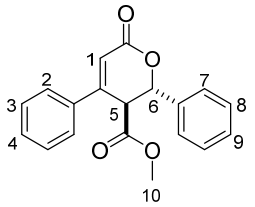


Synthesised according to general procedure M, using anhydrous MTBE (0.1 M, 2.5 mL), freshly distilled benzaldehyde (**135**, 25.0 µL, 0.246 mmol) anhydride **306** (43.3 mg, 0.246 mmol) and catalyst **464** (8.38 mg, 0.0123 mmol - 5 mol%). The reaction was stirred for 5 days to give a diastereomeric mixture of carboxylic acids in a 77:23 ratio (*trans:cis*) in 42% yield which was monitored by ^{1}H NMR spectroscopic analysis using *p*-iodoanisole (28.8 mg, 0.123 mmol). After esterification and purification by flash column chromatography, eluting with 80:20 hexanes:EtOAc, *trans*-**473** was isolated as a yellow oil (24.3 mg, 35%). TLC (hexanes:EtOAc, 8:2 v/v): Rf = 0.34.

δ_H (400 MHz, $CDCl_3$): 7.21-7.02 (6 H, m, H-4, H-5, H-7 and H-8), 6.97 (2 H, d, *J* 7.3, H-3), 6.81 (2 H, d, *J* 7.3, H-6), 6.30 (1 H, s, H-2), 3.78 (3 H, s, H-9), 3.42 (1 H, d, *J* 17.6, H-1b); 3.33 (1 H, d, *J* 17.6, H-1a).

HRMS (ESI): [M+Na] $C_{18}H_{16}O_4Na$ Requires 319.0942 Found 319.0941.

Methyl 6-oxo-2,4-diphenyl-3,6-dihydro-2H-pyran-3-carboxylate (*trans*-**477**, Scheme 5.6)



Synthesised according to general procedure N, using anhydrous MTBE (0.1 M, 2.5 mL), freshly distilled benzaldehyde (**135**, 25.0 μL, 0.246 mmol) and catalyst **474** (9.13 mg, 0.0123 mmol - 5 mol%). The reaction was stirred for 5 days to give a diastereomeric mixture of carboxylic acids in a 95:5 ratio (*trans:cis*). After esterification and purification by flash column chromatography, eluting with 80:20 hexanes:EtOAc, *trans*-**477** was isolated as a pale yellow oil (30.3 mg, 40%, 44% *ee*). TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.69, $[\alpha]_D^{20}$ = -4.5 (*c* = 0.01, $CHCl_3$).

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: *trans*-**477** 20.1 min (major enantiomer) and 24.9 min (minor enantiomer).

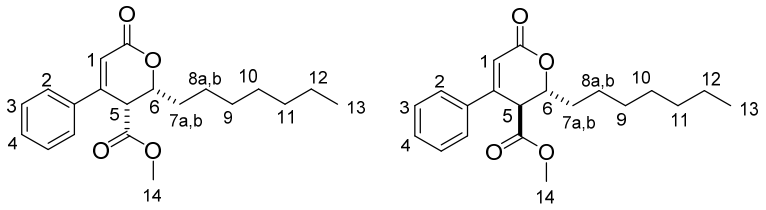
δ_H (400 MHz, $CDCl_3$): 7.46-7.41 (5 H, m, H-2, H-3 and H-4), 7.40-7.32 (5 H, m, H-7, H-8 and H-9), 6.44 (1 H, s, H-1), 6.02 (1 H, d, *J* 4.8, H-6), 4.29 (1 H, d, *J* 4.8, H-5), 3.65 (3 H, s, H-10).

δ_C (100 MHz, $CDCl_3$): 169.6 (C=O), 163.2 (C=O), 151.1, 137.2, 135.7, 130.6, 129.1, 128.83, 128.80, 126.1, 125.9, 117.6, 80.0, 53.0, 49.0.

ν_{max} (neat)/cm^{-1}: 2947, 2850, 1713, 1623, 1517, 1497, 1437, 1353, 1232, 1072, 1088, 973, 828, 766, 697.

HRMS (*m/z* - ESI): $[M+H]^+$ Found: 309.1122 $C_{19}H_{17}O_4$ Requires: 309.1121.

Methyl 2-heptyl-6-oxo-4-phenyl-3,6-dihydro-2H-pyran-3-carboxylate (*cis*-**480**, *trans*-**480**, Table 5.7, entry 1)



Synthesised according to general procedure N, using anhydrous THF (2.4 mL, 0.1 M), freshly distilled octanal (**478**, 38.4 μL, 0.246 mmol) and catalyst **304** (7.85 mg, 0.0123 mmol - 5 mol%). The reaction was stirred for 24 h to give a diastereomeric mixture of carboxylic acids in a 65:35 ratio (*cis*:*trans*). After esterification and purification by flash column chromatography, eluting with 80:20 hexanes:EtOAc, *cis*-**480** and *trans*-**480** were isolated combined as a pale yellow oil (65.0 mg, 80%). TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.59. The enantiomeric excesses of *cis*-**480** and *trans*-**480** were both found to be 99%.

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: *cis*-**480** 17.5 min; *trans*-**480** 22.9 min.

cis-**480**:

δ_H (600 MHz, $CDCl_3$): 7.52-7.45 (2 H, m, H-2), 7.42-7.33 (3 H, m, H-3, H-4), 6.46 (1 H, s, H-1), 4.60 (1 H, ddd, *J* 3.5, 5.1, 8.3, H-6), 3.71 (1 H, d, *J* 3.5, H-5), 3.65 (3 H, s, H-14), 1.88-1.83 (1 H, m, H-7a), 1.84-1.73 (1 H, m, H-7b), 1.70-1.62 (1 H, m, H-8a), 1.58-1.48 (1 H, m, H-8b), 1.40-1.23 (8 H, m, H-9, H-10, H-11 and H-12), 0.94-0.86 (3 H, m, H-13).

δ_C (100 MHz, $CDCl_3$): 168.5 (C=O), 164.8 (C=O), 151.6, 134.8, 130.9, 129.2, 126.1, 116.7, 78.2, 52.9, 47.0, 32.6, 31.7, 29.2, 29.08, 25.3, 22.63, 14.1.

trans-**480**:

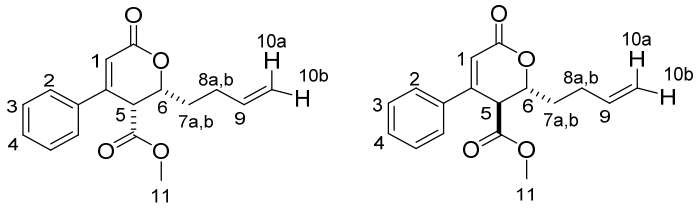
δ_H (600 MHz, $CDCl_3$): 7.42-7.33 (5 H, m, H-2, H-3, H-4), 6.42 (1 H, s, H-1), 4.96-4.88 (1 H, m, H-6), 3.83 (1 H, d, *J* 3.9, H-5), 3.69 (3 H, s, H-14), 1.96-1.89 (1 H, m, H-7a), 1.73-1.64 (1 H, m, H-7b), 1.61-1.51 (1 H, m, H-8a), 1.50-1.42 (1 H, m, H-8b), 1.40-1.23 (8 H, m, H-9, H-10, H-11 and H-12), 0.94-0.86 (3 H, m, H-13).

δ_C (100 MHz, $CDCl_3$): 171.1 (C=O), 163.2 (C=O), 150.9, 134.7, 130.6, 129.1, 126.0, 117.0, 79.2, 53.0, 47.1, 33.8, 31.6, 29.1, 29., 25.4, 22.61, 14.0.

ν_{max} (neat)/cm^{-1}: 2927, 2856, 1712, 1624, 1447, 1350, 1242, 1161, 1020, 875, 772, 726, 686.

HRMS (*m/z* - APCI): $[M+H]^+$ Found: 331.1913 $C_{20}H_{27}O_4$ Requires: 331.1903.

Methyl-2-(4-methylpent-3-en-1-yl)-6-oxo-4-phenyl-3,6-dihydro-2H-pyran-3-carboxylate (*cis*-**481**, *trans*-**481**, Table 5.7, entry 3)



Synthesised according to general procedure N, using anhydrous THF (0.1 M, 2.4 mL), freshly distilled 4-pentenal (**479**, 24.3 µL, 0.246 mmol) and catalyst **304** (7.85 mg, 0.0123 mmol - 5 mol%). The reaction was stirred for 24 h to give a diastereomeric mixture of carboxylic acids in a 56:44 ratio (*cis*:*trans*). After esterification and purification by flash column chromatography, eluting with 80:20 hexanes:EtOAc, *cis*-**481** and *trans*-**481** were isolated combined as a pale yellow oil (56.3 mg, 81%). TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.72. The enantiomeric excesses of *cis*-**481** and *trans*-**481** were both found to be 99%.

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: *cis*-**481** 37.6 min; *trans*-**481** 27.1 min.

cis-**481**:

δ_H (600 MHz, $CDCl_3$): 7.61-7.54 (2 H, m, H-2), 7.53-7.41 (3 H, m, H-3 and H-4), 6.56 (1 H, s, H-1), 5.95-5.76 (1 H, m, H-9), 5.15 (1 H, dd, *J* 1.5, 17.6, H-10a), 5.07 (1 H, dd, *J* 1.5, 10.2, H-10b), 4.62 (1 H, ddd, *J* 3.4, 4.9, 8.7, H-6), 3.80 (1 H, d, *J* 3.4, H-5), 3.75 (3 H, s, H-11), 2.48-2.39 (1 H, m, H-8a), 2.40-2.31 (1 H, m, H-8b), 2.02-1.93 (1H, m, H-7a), 1.93-1.84 (1 H, m, H-7b).

δ_C (100 MHz, $CDCl_3$): 169.4 (C=O), 164.6 (C=O), 151.5, 136.7, 134.7, 131.1, 129.1, 126.1, 116.7, 116.2, 77.2, 52.9, 46.9, 31.7, 29.3.

trans-**481**:

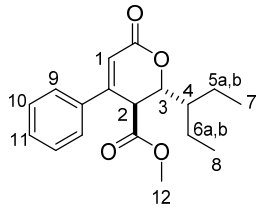
δ_H (600 MHz, $CDCl_3$): 7.53-7.41 (5 H, m, H-2, H-3 and H-4), 6.44 (1 H, s, H-1), 5.86-5.77 (1 H, m, H-9), 5.12 (1 H, dd, *J* 1.5, 17.1, H-10a), 5.06 (1 H, dd, *J* 1.5, 10.1, H-10b), 4.98-4.93 (1 H, m, H-6), 3.86 (1 H, d, *J* 4.1, H-5), 3.69 (3 H, s, H-11), 2.40-2.33 (1 H, m, H-8a), 2.32-2.23 (1 H, m, H-8b), 2.12-1.98 (1H, m, H-7a), 1.82-1.70 (1 H, m, H-7b).

δ_C (100 MHz, $CDCl_3$): 169.9 (C=O), 162.9 (C=O), 150.9, 136.5, 135.8, 130.7, 129.4, 126.0, 117.0, 116.21, 78.4, 53.1, 47.2, 33.1, 29.4.

ν_{max} (neat)/cm^{-1}: 2952, 1710, 1641, 1447, 1352, 1255, 1118, 1055, 973, 909, 878, 774, 683, 603.

HRMS (*m/z* - APCI): $[M+H]^+$ Found: 287.1277 $C_{17}H_{19}O_4$ Requires: 287.1277.

Methyl 6-oxo-2-(pentan-3-yl)-4-phenyl-3,6-dihydro-2H-pyran-3-carboxylate (*trans*-**447**, Table 5.8, entry 2)



Synthesised according to procedure N, using anhydrous THF (0.1 M, 2.4 mL), 2-ethylbutyraldehyde (**403**, 30.4 µL, 0.246 mmol) and catalyst **304** (7.85 mg, 0.0123 mmol

- 5 mol%). The reaction was stirred for 24 h to give a diastereomeric mixture of carboxylic acids in a 50:50 ratio (*cis*:*trans*). After esterification and purification by flash column chromatography, eluting with 80:20 hexanes:EtOAc, *cis*-**447** and *trans*-**447** were isolated as a white solid (67.0 mg, 90%). TLC (hexanes/EtOAc, 8:2 *v/v*): R_f = 0.59. The enantiomeric excesses of *cis*-**447** and *trans*-**447** were both found to be 99%.

CSP-HPLC analysis. Chiralcel OD (4.6 mm x 25 cm), hexane/IPA: 90/10, 0.3 mL min^{-1}, RT, UV detection at 254 nm, retention times: *cis*-**447** 55.7 min; *trans*-**447** 55.2 min.

trans-**447**:

δ_H (400 MHz, $CDCl_3$): 7.60-7.59 (2 H, m, H-10), 7.50-7.47 (3 H, m, H-9 and H-11), 6.42 (1 H, s, H-1), 4.83 (1 H, dd, *J* 4.4, 7.3, H-3), 4.03 (1 H, d, *J* 4.4, H-2), 3.61 (3 H, s, H-12), 1.84.1.69 (3 H, m, H-4, H-5a, H-6a), 1.70-1.62 (1 H, m, H-5b), 1.53-1.44 (1 H, m, H-6b), 0.98-0.94 (6 H, m, H-7 and H-8).

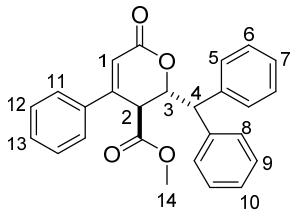
δ_c (100 MHz, $CDCl_3$): 170.0 (C=O), 163.4 (C=O), 152.3, 135.9, 130.5, 129.1 129.2, 126.0, 117.3, 81.0, 44.9, 43.1, 22.0, 21.0, 10.7, 10.5.

ν_{max} (neat)/cm^{-1}: 3086, 2965, 2877, 1721, 1696, 1446, 1353, 1269, 1245, 1086, 1012, 990, 893, 777, 689, 602, 576.

HRMS (*m/z* -APCI): $[M+H]^+$ Found: 303.1598 $C_{18}H_{23}O_4$ Requires: 303.1590.

(See page 230 for characterisation of *cis*-**447**).

Methyl 2-benzhydryl-6-oxo-4-phenyl-3,6-dihydro-2H-pyran-3-carboxylate (*trans*-**442**, Table 5.8, entry 4)



Synthesised according to general procedure N, using anhydrous THF (0.1 M, 2.4 mL), freshly distilled diphenylacetaldehyde (**440**, 43.6 μL, 0.25 mmol) and catalyst **304** (7.8 mg, 0.0123 mmol - 5 mol%). The reaction was stirred for 24 h to give a diastereomeric

mixture of carboxylic acids in a 52:48 ratio (*trans*:*cis*). After esterification and purification by flash column chromatography, eluting with 80:20 hexanes:EtOAc, *trans*-**442** and *cis*-**442** were isolated combined as a pale yellow oil (88.2 mg, 90%). TLC (hexanes/EtOAc, 8:2 *v/v*): R_f 0.67. The enantiomeric excesses of *cis*-**442** and *trans*-**442** were both found to be 99%.

CSP-HPLC analysis. ACQUITY UPC^2, Trefoil AMY1, 2.5µm (3.0 x 150mm). ABPR: 1500 (psi). A (CO_2) = 97%/B (Ethanol/CAN/IPA 1:1:1, *v:v*) = 3%, 1.2 mL min^{-1}, 30 °C, UV detection at 254 nm, retention times: *trans*-**442** 3.0 min; *cis*-**442** 2.9 min.

trans-**442**:

δ_H (400 MHz, $CDCl_3$): 7.49-7.45 (2 H, m, H-11), 7.44-7.39 (5 H, m, H-5, H-12 and H-13),7.38-7.35 (4 H, m, H-8 and H-9),7.35-7.29 (3 H, m, H-6 and H-10), 7.21-7.19 (1 H, m, H-7), 6.53 (1 H, s, H-1), 5.83 (1 H, dd, *J* 2.9, 10.4, H-3), 4.34 (1 H, d, *J* 10.4, H-4), 3.83 (1 H, d, *J* 2.9, H-2), 3.67 (3 H, s, H-14).

δ_C (100 MHz, $CDCl_3$): 169.7 (C=O), 162.4 (C=O), 150.3, 140.6, 139.5, 135.7, 130.7, 129.4, 129.0, 128.8, 128.4, 128.1, 127.6, 127.2, 126.3, 116.9, 80.6, 54.4, 53.1, 44.3.

ν_{max} (neat)/cm^{-1}: 3088, 2971, 2923, 1660, 1592, 1506, 1472, 1311, 1217, 1072, 998, 768, 642.

HRMS (m/z -ESI): $[M+Na]^+$ Found: 421.1407 $C_{26}H_{22}O_4Na$ Requires: 421.1410.

(See page 228 for characterisation of *cis*-**442**).

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